UNIVERSITY OF TORONTO
MEDICAL JOURNAL

You, Your Stethoscope, and the Heart	J. D. Morin	178
Hypertension due to Unilateral Renal Disease	D. R. Wilson	183
The Mind, the Pathway, and the Body	H. Newton	188
Neonatal Hepatitis	J. E. Milligan	192
The Oral Hypoglycemic Agents	J. E. Harris	197
Hypofunction of the Adrenal Cortex in Infancy	J. Hoffman	203
Bronchiectasis	C. G. Gonsalves	209
Embers	C. S. S.	215
Abstracts		216
News and Notes		217

APRIL 1959

VOLUME XXXVI NUMBER 6

a MAJOR neuroleptic in Psychiatry

NOZINAN

levomepromazine (R.P.7044)

TABLETS 5 mg., 25 mg., 50 mg.

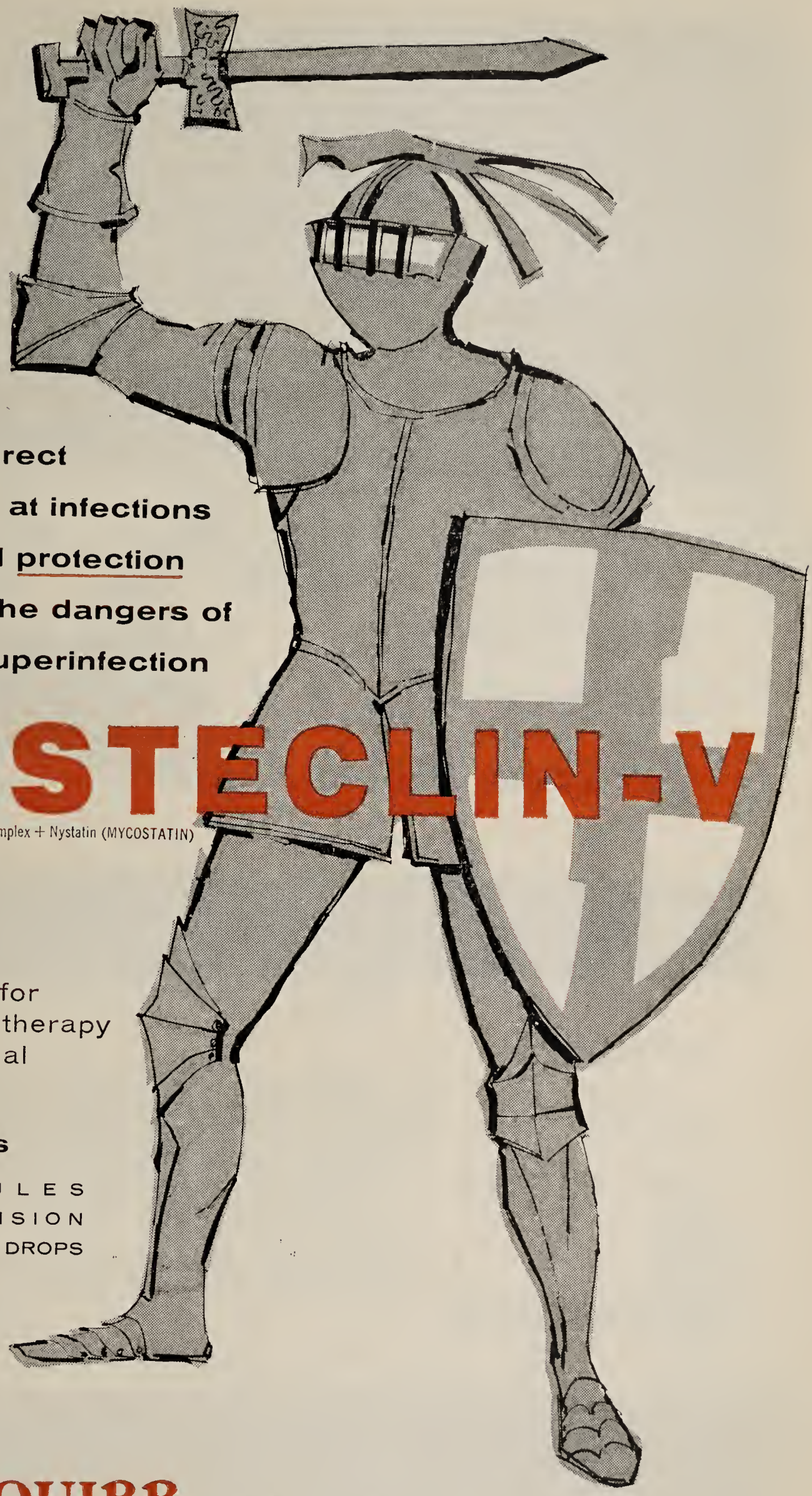
AMPOULES 1 ml., 25 mg.
2 ml., 5 mg. per ml.

EXTENSION OF THE CLINICAL APPLICATIONS OF LARGACTIL

SELECTIVE ACTION
in severe depressive conditions of the melancholic type

literature and
samples upon request

Poulenc



For a direct strike at infections plus added protection against the dangers of monilial superinfection

MYSTECLIN-V

Squibb Tetracycline Phosphate Complex + Nystatin (MYCOSTATIN)

The logical combination for antibacterial therapy plus antifungal prophylaxis

AVAILABLE AS

CAPSULES
SUSPENSION
PEDIATRIC DROPS

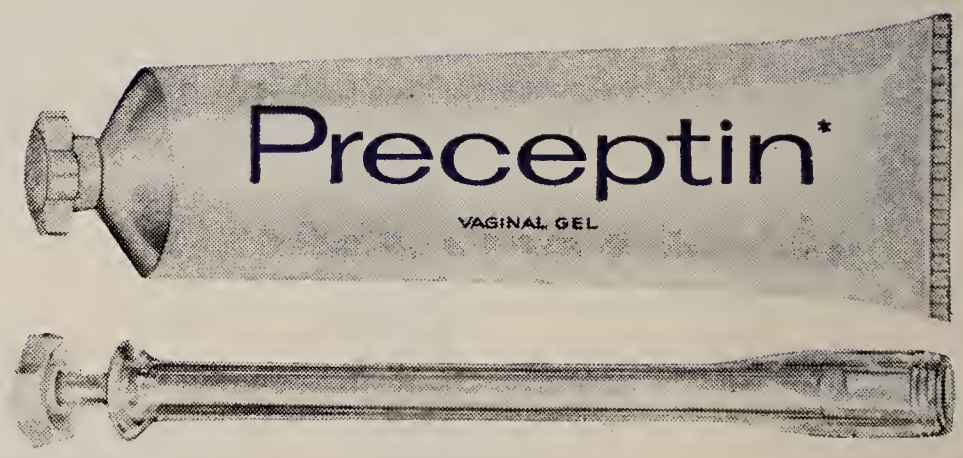
SQUIBB *A Century of Experience Builds Faith*

MYSTECLIN AND MYCOSTATIN ARE REGISTERED SQUIBB TRADEMARKS

. . . consistently effective
esthetically acceptable

when a diaphragm is preferred
Ortho Kit*

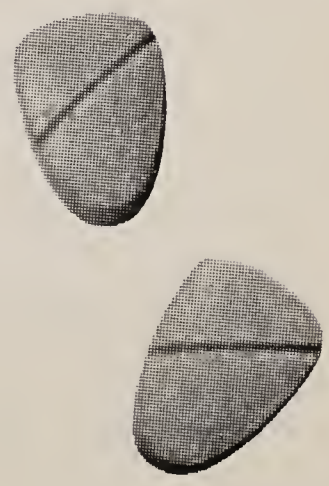
when a gel alone is preferred



more than

15,000

Canadian DIABETICS now experience GREATER FREEDOM and generally BETTER CONTROL on oral management with



Mobenol

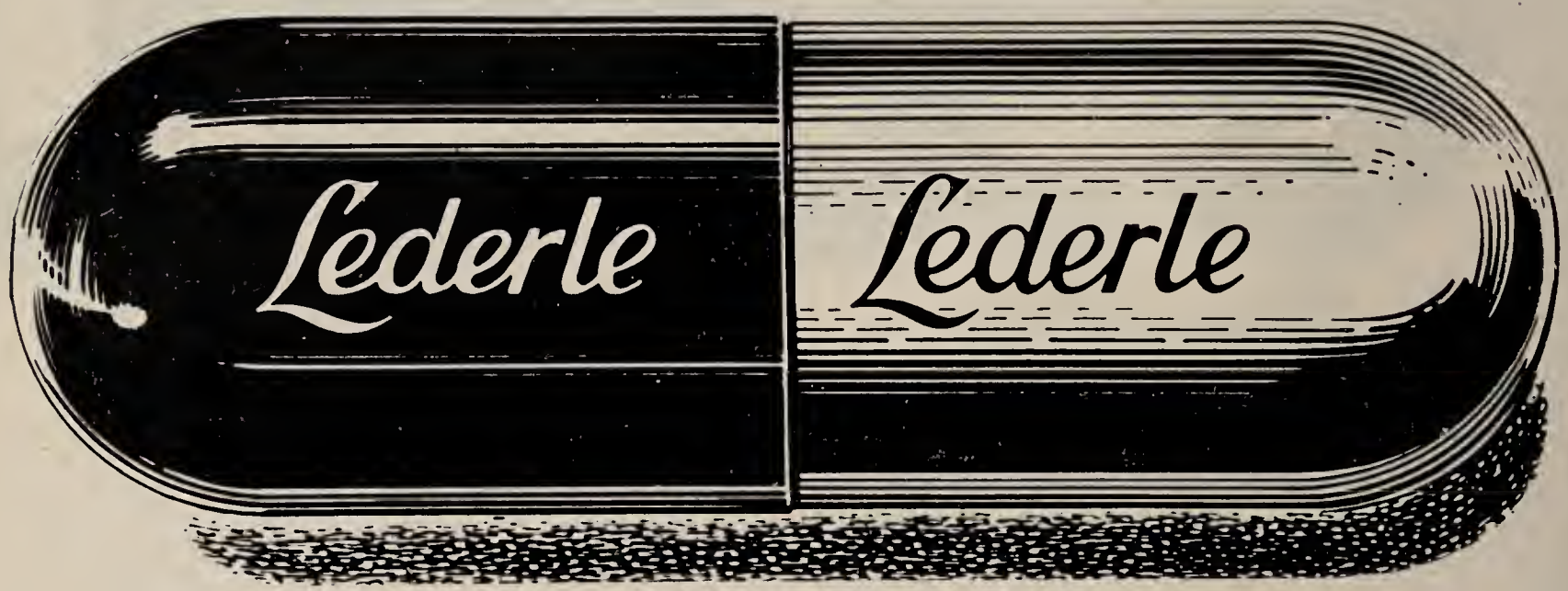
mobilizes endogenous insulin*

SUPPLY: Mobenol — (tolbutamide, Horner)
50 orange 0.5 Gm. tablets per bottle.

*Goetz, F.C. and Egdahl, R.H., Fed. Proc. 17:55, 1958

FRANK W. HORNER LIMITED • MONTREAL CANADA

in
this capsule
lives the
most widely
used



the most
widely useful
antibiotic
in the
world
Achromycin® V

Tetracycline with
Citric Acid Lederle

SUPPLIED IN CAPSULES OF 250 MG.
WITH 250 MG. CITRIC ACID,
AND 100 MG. WITH 100 MG. CITRIC ACID

Lederle
CANADA

® Reg. Trademark in Canada

LEDERLE LABORATORIES DIVISION, CYANAMID OF CANADA LTD., Montreal, Quebec

Baby's Own Tablets

satisfactorily relieved

every one of 40 babies* with

constipation

and 34 out of 35 babies* with

teething

gastrointestinal upset and malaise

with complete easing of straining at stool, gas distress, disturbed sleep, restlessness, crankiness and anorexia.

REMARKABLY SAFE — "Throughout the study . . . in no instance was there any untoward reaction" whatsoever.

BABY'S OWN TABLETS provide Phenolphthalein 3/16 grain, mildly buffered with Precipitated Calcium Carbonate ½ grain, and Powdered Sugar q.s. Pleasant, convenient.

*2 months to 24 months of age.

For a sample supply and literature citing references 1-15 write . . .

Typical Case History

CASE #50. Baby R.S., age 12 months, weight 20 lb. 10 oz., had gastrointestinal discomfort and malaise associated with teething. Baby had no teeth as yet, but gums were tender, puffy and swollen. Baby was cranky, irritable, restless and couldn't sleep. Drooling was excessive; appetite poor.

BABY'S OWN TABLETS were given, one each night at bedtime.

Baby had satisfactory relief of symptoms. Appetite improved. First days, then nights, became more comfortable. Baby now has six teeth.

G. T. FULFORD CO., LIMITED, Brockville, Ontario

STELAZINE*

A FURTHER ADVANCE IN PSYCHOPHARMACOLOGY

Smith Kline & French has for many years been engaged in a continuous program of psychopharmacological research. Many hundreds of compounds have been tested by our laboratory scientists, in a ceaseless effort to improve upon existing drugs and to discover new ones. During the past decade our procedures for the pharmacological screening of neuroleptic agents have become highly refined; only a compound which exhibits characteristics marking it as a distinct therapeutic or pharmaceutical advance can survive this stringent process of elimination.

The latest product of our research in this area is 'Stelazine' (trifluoperazine, S.K.F.), a promising tranquilizer and antiemetic which has so far been clinically proved in over 10,000 patients. Its chemical formula is 10-[3-(1-methyl-4-piperazinyl) propyl]-2-trifluoromethylphenothiazine.

'Stelazine' appears to be the safest and most potent of the known phenothiazine derivatives, a growing group of compounds recently developed to aid the victims of mental illness.

• In doses of 2 to 4 mg. per day, 'Stelazine' has proved highly effective in the treatment of mild to moderate mental and emotional disorders, as well as for the control of nausea and vomiting from a wide variety of causes.

• With psychotic patients, clinicians have found 'Stelazine' to be of outstanding value, in a dosage range of from 5 to 20 mg. a day. It has produced remarkable improvement in many withdrawn, apathetic schizophrenics, and has often helped patients who have been refractory to previous therapies.

SMITH KLINE & FRENCH · MONTREAL 9

9227

*Reg. Can. T. M. Off.

UNIVERSITY OF TORONTO MEDICAL JOURNAL

ESTABLISHED DECEMBER 1923
AN UNDERGRADUATE PUBLICATION

VOLUME XXXVI NUMBER 6

TORONTO, APRIL 1959

Editor-in-Chief . . . . . P. C. F. Moore, 5T9

Associate Editor . . . . . P. B. Dent, 6T0

Assistant Editor . . . . . R. F. Armstrong, 5T9

Business Manager . . . . . J. R. Lundon, 6T0

Advertising Manager . . . . . R. D. J. Brand, 6T2

Assistant Advertising Manager . . . . . Miss J. Sikimba, 6T2

Circulation Manager . . . . . G. V. Boujoff, 6T2

This Journal is published six times a year from November to April, by the Medical Society of the University of Toronto, to serve primarily as a medium for student expression.

Subscription rates: $3.50 for one volume of six consecutive issues. Single copies 65¢.

Manuscripts including references and footnotes should be typewritten double spaced on one side of the paper. References should be kept to a minimum, and should be cited numerically in the order in which they appear in the text.

Manuscripts in excess of 3,000 words will be considered *unsatisfactory*.

Illustrations are included by arrangement with the Editor. Drawings should be done on white paper in black ink.

Final copy date is the first day of *two months* prior to publication, e.g., September 1 for the November issue.

Material printed in this Journal is covered by copyright. Papers are accepted for consideration with the understanding that they are contributed for publication in this Journal only.

Correspondence should be addressed to Room 114, Medical Building, University of Toronto, Toronto 5, Ontario.

Authorized as Second Class Mail, Post Office Department, Ottawa.

YOU, YOUR STETHOSCOPE, AND THE HEART

J. D. MORIN, 5T9

SINCE the stethoscope has almost replaced the Caduceus as a symbol of the medical profession, it behooves the medical practitioner to use it intelligently and to interpret correctly the findings it uncovers. Certain new techniques such as phonocardiography and intracardiac catheterization have increased our knowledge and enabled us to evaluate better the significance of cardiac sounds and murmurs, and to associate them more correctly with cardiovascular changes.

History

Until the 16th century little attention had been given to the heart and its function. In 1616, William Harvey, a mediaeval physician gave a series of "visceral lectures" in which he compared the heart sounds to "two clacks of watter bellows to rayse watter." Here, and in his famous *De Motu Cordis* are some of the earliest references to heart sounds. From that time on interest in the heart grew and in 1819 the ingenious Rene Laennec devised a new technique of auscultation with a rolled quire of paper which enabled him to hear the heart sounds much better. This primitive stethoscope did not last long and it was soon replaced by rigid tubes of various shapes and sizes. The examiner would put one end in his ear and the other on the chest of the patient. In 1885 the modern-day stethoscope was developed by George P. Cammann. The original had flexible tubing, binaural ear pieces and a bell head and can be seen in the Museum of American Armed Forces Institute of Pathology, Washington, D.C.

Technique

Good auscultation requires the best of conditions. Even with a modern stethoscope with the standard combination head, the maximum findings can only be obtained if there is a quiet room where both examiner and patient are comfortable. The patient should be stripped to the waist, kept warm and not allowed to get cold or shiver. Various postures and various phases of respiration should be tried in auscultating the heart. One should listen to the four principal areas for accurate assessment. These are:

(1) aortic area—2nd right intercostal space at the sternal margin
(2) pulmonic area—2nd left intercostal space at sternal margin
(3) tricuspid area—lower left sternal border (4th left intercostal space)
(4) apex area—at apex beat or 5th intercostal space in midclavicular line.

In equivocal cases it is wise to check other areas as:

(1) base of neck (re aortic stenosis)
(2) Erb's area: 3rd left intercostal space while sitting leaning forward in expiration (re aortic regurgitation)
(3) apex in left lateral decubitus position after exercise (re mitral stenosis)
(4) right sternal border (re aortic regurgitation)

Prolonged auscultation is not good and frequent short periods concentrating on the various phases of cycle and components of cycle is the more desirable technique.

Heart Sounds

etiology:

Normal heart sounds have been attributed to many causes. The current belief is that they are due to the closure of the appropriate valves.

The first sound (S_1) is due to the

closing of the mitral and tricuspid valves while the second sound is due to the closure of the aortic and pulmonic valves. In both instances the sounds are due to the abrupt blowing out of the valve curtain. The third heart sound often heard is due to ventricular filling and alteration in the volume elasticity of the ventricle.

The cardiac cycle is divided into systole and diastole. Systole is considered as the period of ventricular contraction or roughly that period between atrio-ventricular valve closure and ventricular-vessel valve closure. In other words, the period between S_1 and S_2 is systole. Diastole is the resting phase or the period between S_2 and S_1.

In figure one the atrial and ventricular pressures are recorded in relation to the cardiac cycle. The systemic pressure is also recorded. The valves function according to pressure gradients, opening and closing as the pressures within the chambers rise and fall in relation to the connecting chambers. Timing of the sounds can be assisted by palpating the carotid pulse, as S_1 and carotid pulsation occur simultaneously.

CHARACTERISTICS OF THE SOUNDS

Normally the first sound is *dull* and prolonged and heard best in the tricuspid and mitral areas.

The second sound is sharper in quality and heard best in aortic and pulmonary areas. In childhood and youth P_2 is usually greater than A_2 while in adults the converse is true. A_2 is greater than P_2. In the aortic area the second sound is usually single while splitting is usually heard in the pulmonary area.

The first sound seldom splits but if it does it usually does in complete right bundle branch block which causes a delayed contraction of the right ventricle and closure of tricuspid valve.

The second sound may split normally and the splitting in normal cases widens with inspiration. If the splitting does not widen with inspiration but remains equal or fixed, then it is pathological. This occurs in mitral regurgitation, complete right bundle branch block, atrial septal defect, anomalous vein, or any left to right shunt that causes increased right ventricular flow and a delayed closure of the pulmonary valve.

In severe pulmonary stenosis there is likely to be either an inaudible or faint second sound in the pulmonary area, for the aortic component is masked by the systolic murmur, while in the tetralogy of Fallot, there is always a pulmonary second sound.

Reversed splitting is seen in prolongation of left ventricular systole when the aortic valve closes after the pulmonary valve. It is determined by having the patient breathe normally. If present, the splitting will be maximum during expiration and minimum with inspiration. This is seen with complete left bundle branch block, aortic stenosis and hypertension.

The *intensity* of the sound varies with certain states. The first sound is maximum if the flow is continuous throughout diastole and the valves are wide open. This occurs in mitral and tricuspid stenosis.

The second sound is increased in pulmonary or systemic hypertension.

The sounds may be increased in high output states as pregnancy, thyrotoxicosis and anaemia while all the sounds will be decreased in pericardial effusion and often with failure and/or myocardial infarcts.

TYPES OF SOUNDS HEARD:

Ejection Sounds

The ejection of blood into a dilated pulmonary artery or aorta often causes sharp clicking sounds early in systole.

The pulmonary ejection click occurs in the pulmonary area, decreases with inspiration and occurs with a dilated pulmonary artery as with pulmonary stenosis or pulmonary hypertension of any type.

The aortic ejection sounds are heard in aortic stenosis, aortic regurgitation, coarctation, aneurysm and with hypertension. These are not affected by inspiration and often occur at the apex.

Third Heart Sounds

As mentioned, there is a physiological third heart sound heard. This can be present normally up to the age of forty. After forty the third sound is often heard late in diastole as a gallop rhythm. This occurs in left ventricular failure, mitral regurgitation and constrictive pericarditis. It suggests a grave prognosis.

Opening Snaps

These occur with mitral stenosis. It is due to the flapping of the stenotic mitral valve which is like a diaphragm. The opening snap is best heard in the apical region and it is high pitched and heard in early diastole. It is difficult to distinguish from a splitting second sound and from the third heart sounds. This can be done by checking the pulmonary area and aortic area or phonocardiographically.

Murmurs

The cause of murmurs is becoming more clearly understood. Many factors such as turbulence, relation of volume of flow to size of orifice and possibly cavitation play a part in producing that noise known as a murmur.

Murmurs are of two varieties, organic, meaning associated with a pathological entity, and functional, being related to no structural abnormality.

A functional murmur has the following characteristics:

1. systolic
2. in 2nd, 3rd and 4th left costal interspace along left sternal margin.
3. occurs early in systole
4. exaggerated by exercise
5. loudest in supine position
6. no change in heart sounds
7. heard usually in pulmonary area
8. faint and low frequency
9. transient course, disappears in time.

Systolic Murmur

There are two types of systolic murmurs. There is the (a) mid systolic ejection type and (b) the pansystolic regurgitant types.

The mid systolic ejection type occurs between S_1 and S_2 starting just after S_1 and having a mid systolic accentuation.

This is the type of murmur seen with aortic stenosis or pulmonary stenosis. These are usually harsh murmurs but can be softened by a reduction in cardiac output as in cardiac failure or mitral regurgitation in association with aortic stenosis.

Basal ejection murmurs are due to increased stroke output with anaemia, thyrotoxicosis, pregnancy or heart block.

Pansystolic Regurgitation Murmur

These murmurs carry right through systole beyond the second sound and often drown out the second aortic sound.

These murmurs occur in mitral or tricuspid regurgitation. As well they occur with left or right shunts as ventricular septal defects and occasionally in patent ductus arteriosus.

Diastolic Murmurs

There are two types—(a) ventricular filling murmur and (b) aortic or pulmonary regurgitant murmur.

The ventricular filling murmur is the murmur that occurs in mitral stenosis or valvulitis. As well these murmurs occur with patent ductus, ventricular septal defect and tricuspid stenosis. These murmurs start early or late in diastole and can be *crescendo* in nature with presystolic accentuation. This accentuation is due to atrial systole and it may be absent in atrial flutter or fibrillation. These murmurs are usually low pitched rumbling sounds heard best with a bell stethoscope pressed lightly against the skin.

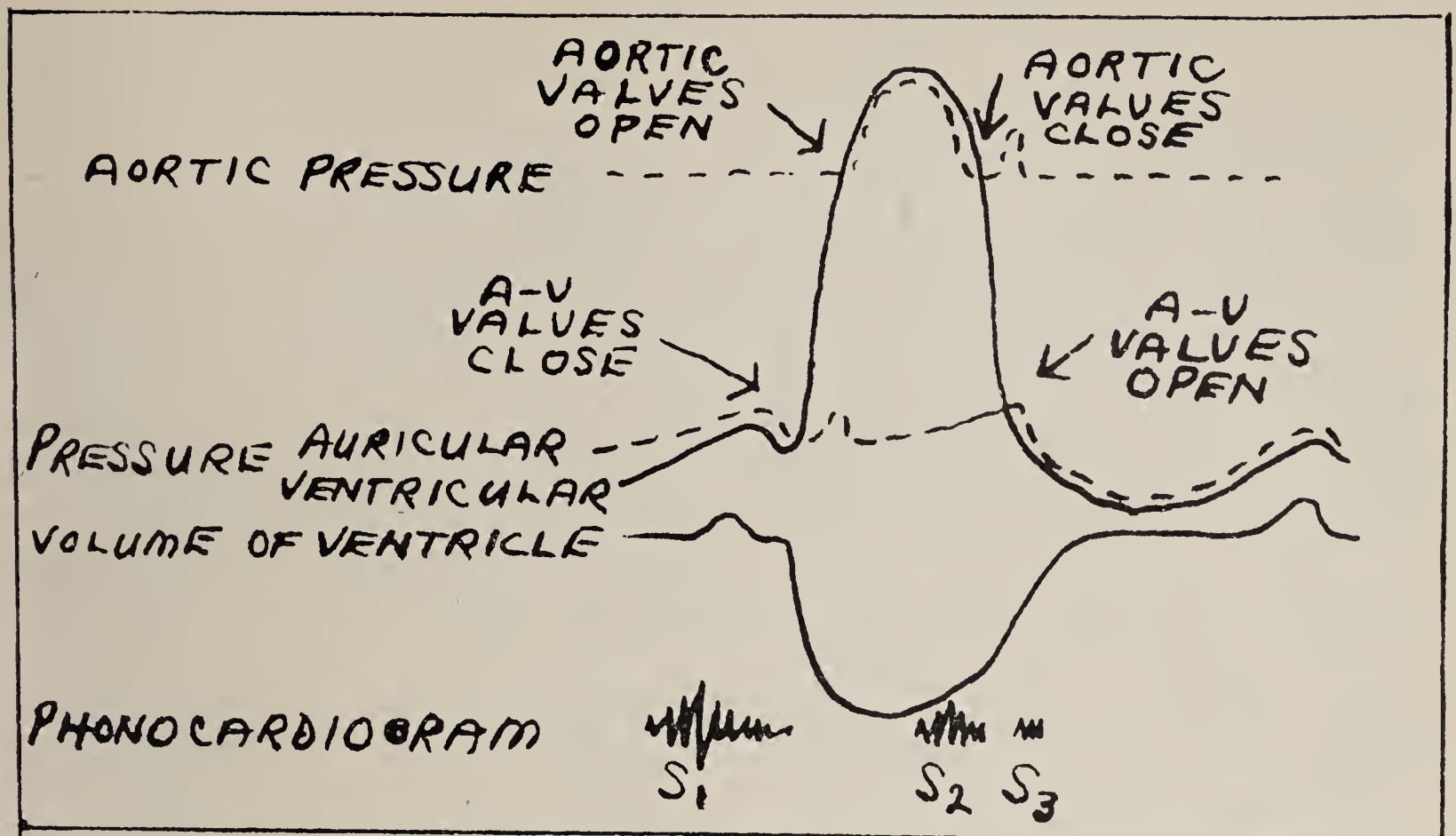


FIGURE ONE

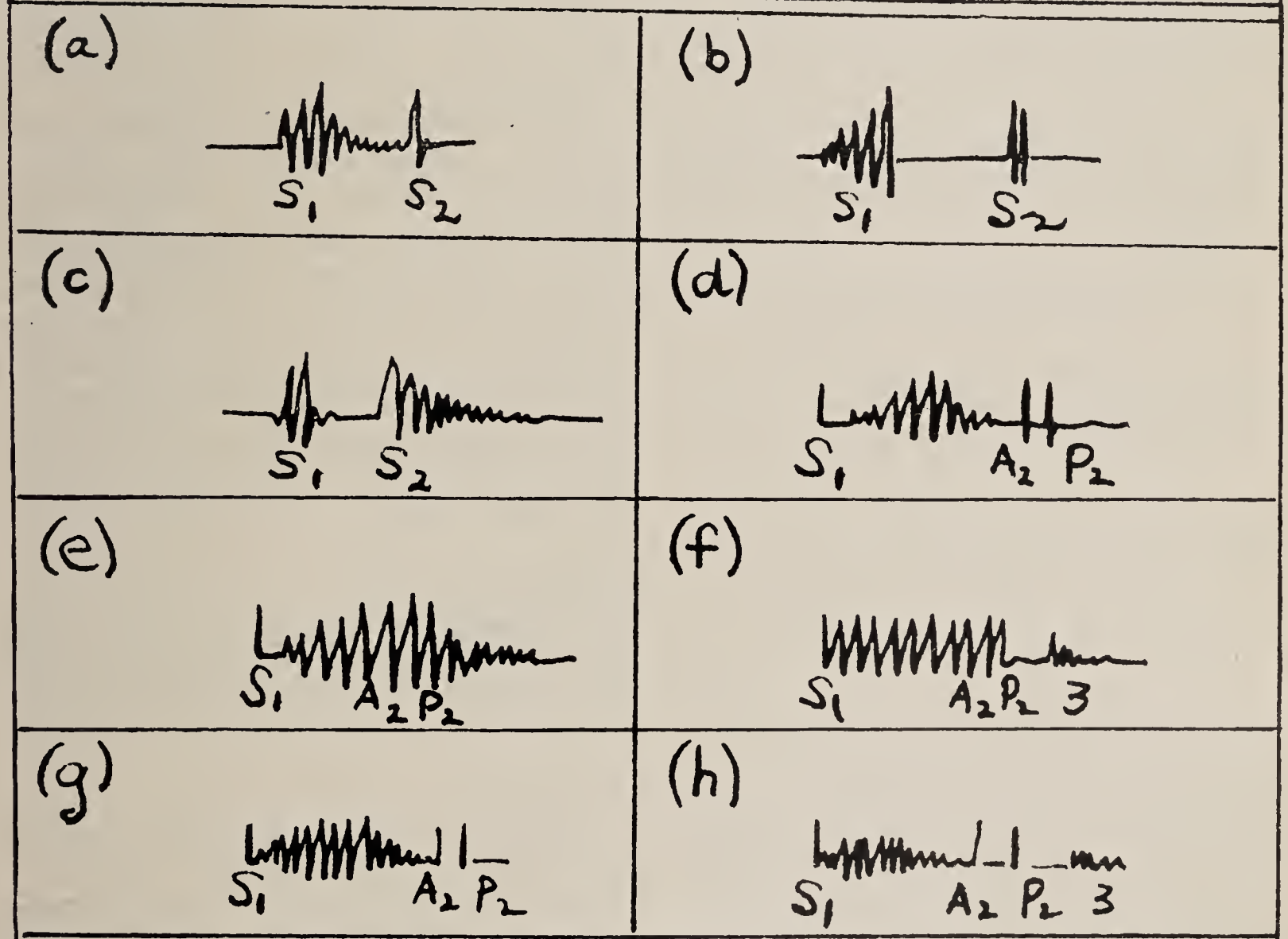


FIGURE TWO

Aortic or Pulmonary Regurgitant Murmurs

These are crescendo in type, the crescendo being early in diastole.

The murmurs produce a *wfff* sound and usually have a high frequency. They are usually seen with aortic regurgitation or pulmonary regurgitation and are very hard to differentiate. Mitral stenosis can be differentiated by the following increase in the first mitral sound, a low rumbling murmur and an increase in P_2.

EXAMPLES:

Relating ausculatory findings to common conditions is the job of the clinician. Here are some graphic examples:

Mitral Insufficiency: (Fig. 2 (a))
1. at apex
2. blowing
3. systolic
4. transmitted to axilla
5. S_1 is softened.

Mitral Stenosis: (Fig. 2 (b))
1. heard at apex with patient lying on left side
2. diastolic
3. rumbling
4. presystolic accentuation
5. M_1 accentuated, P_2 accentuated.

Aortic Insufficiency: (Fig. 2 (c))
1. heard down left sternal border
2. diastolic discrescendo
3. *wfff* sound.

Aortic Stenosis: (Fig. 2 (d))
1. heard in aortic area
2. transmitted into neck or right side
3. systolic ejection
4. harsh
5. S_1 accentuated at apex, click.

Patent Ductus Arteriosus: (Fig. 2 (e))
1. heard over precordium
2. continuous throughout diastole and systole
3. crescendo, then discrescendo around S_2.

Ventricular Septal Defect: (Fig. 2 (f))
1. heard over precordium—maximum in 3rd and 4th interspaces near left sternal border
2. transmitted to back and epigastrium
3. systolic
4. loud and harsh
5. S_2 split.

Pulmonary Stenosis: (Fig. 2 (g))
1. in pulmonary area
2. systolic ejection
3. mid systolic accentuation
4. P_2 split or absent
5. A_2 may be absent
6. Click.

Coarctation of the Aorta
1. heard down left sternal border
2. transmitted to back beneath scapulae
3. occurs late in systole and even in diastole
4. faint
5. P_2 accentuated.

Atrial Septal Defect: (Fig. 2 (h))
1. occurs in 2nd and 3rd left interspaces
2. systolic
3. S_1 may be split inside apex. S_2 always wide split
4. third sound audible
5. Click common.

CONCLUSION

One should not attempt spot diagnosis with auscultation alone. Only after a thorough work-up with a history, complete physical examination and investigation can one come to a sensible conclusion. Here we have emphasized those features in the auscultatory examination of the heart which are likely to help to lead us to the correct diagnosis and these are supplemented with some graphic examples.

ACKNOWLEDGEMENT

I should like to thank Dr. R. D. Rowe of the Hospital for Sick Children for his kind help and suggestions in the preparation of this paper.

BIBLIOGRAPHY

1. Physiological Basis of Medical Practice. Best and Taylor, Chapter 21.
2. Paed. Clin. of N. A., Nov., 1958. Ausc. of the Heart—A. Leatham, M.D.
3. Cardiovascular Sound in Health and Disease, V. H. McKusick.
4. Heart Disease in Infancy and Childhood —Keith, Rowe, Vlad.

HYPERTENSION DUE TO UNILATERAL RENAL DISEASE

D. R. WILSON, 5T9

Classification of Hypertension:

COMBINED systolic and diastolic (systemic) hypertension may be roughly divided into two large groups, namely primary (or essential) and secondary.

The list of factors responsible for so-called secondary hypertension is gradually being expanded, and Harrison divides it into four large groups. These groups are as follows:

1. Unilateral renal disease (which we shall expand upon).
2. Endocrine disorders, e.g., Cushing's syndrome, primary hyperaldosteronism, pheochromocytoma.
3. Neurogenic causes, e.g., rapidly expanding brain tumour.
4. Miscellaneous lesions, e.g., coarctation of the aorta, polycythemia.

By primary hypertension we mean essential (or idiopathic) hypertension. Many etiological factors have been implicated in this disease, but its basic causation is still not clear. It may be subdivided into benign and malignant (or accelerated) phases. The diagnosis of the latter is established by several criteria such as high levels of diastolic pressure (with or without the rapid onset of symptoms), the development of papilledema and progressive renal failure. The curable hypertension may also have a malignant phase and it is important to remember that it often presents as such.

The Significance of the Problem:

Essential hypertension accounts for 90–95% of all cases of hypertension. However in many instances we cannot accept this diagnosis until other diseases have been ruled out. Renal disease accounts for most of the remaining cases, with Cushing's syndrome and coarctation being the other common secondary types. This renal disease is usually bilateral, with pyelonephritis or glomerulonephritis being responsible. Thus we see that unilateral renal disease is an infrequent cause of hypertension, but it is not rare and, with new techniques, is being diagnosed more frequently. It is of importance for three reasons:

1. It was discovered as the result of the Goldblatt experiments. It was then found clinically; when diagnosed, can often be cured by nephrectomy.
2. It often causes such a severe degree of hypertension that the patient would have died if not diagnosed and treated.
3. The cure which may result is proof that human hypertension can be directly caused by kidney disease and that the effects of hypertension may be reversible.

Etiology and Pathology:

A classification of the types of unilateral renal disease which may give rise to hypertension is as follows:

1. Lesions of the renal vessels (or aorta at the origin of the renal vessels).
2. Lesions of the renal parenchyma.
3. Perinephric lesions.
4. Obstructive lesions of the urinary tract.

Perinephric abscesses, hematomas or tumours are rare causes of hypertension. They correspond to the experimental cellophane wrapping of one kidney which acts as an irritant and may produce hypertension in animals.

Unilateral obstructive lesions such as ureteral stone, stricture or tumour may produce hypertension indirectly by causing unilateral hydronephrosis and

pyonephrosis. Obstructive lesions affecting both kidneys such as prostatic hypertrophy or urethral stricture are more commonly associated with hypertension than are the unilateral lesions.

Pyelonephritis (renal parenchyma) is a common cause of hypertension secondary to renal disease. Pathologically, pyelonephritis is always bilateral, although not necessarily symmetrical. Clinically, however, it may appear to be mainly unilateral as revealed by various investigations of renal function. The removal of such an atrophic kidney resulted in cure of the hypertension in only about 25% of cases. These poor results were due to the lack of sensitivity of the tests used at this time which resulted in failure to detect disease in the other kidney. The outcome was that unilateral nephrectomy for hypertension due to so-called unilateral pyelonephritis fell into relative disfavour. Other unilateral parenchymal diseases which may be responsible for hypertension are a congenital polycystic kidney, a renal tumour, or even a traumatic rupture of a kidney.

Lesions of the renal vessels are becoming more important because of the two new diagnostic techniques of abdominal aortography and differential sodium excretion which will be outlined later. The essential physiological disturbance is renal ischemia. This can occur as the result of partial occlusion of one or both main renal arteries in the aorta or in the artery itself, or as the result of complete occlusion of one of the main branches, or of an anomalous renal artery. The pathological processes which may be responsible for the occlusion are many: (1) in the aorta, thrombosis or dissecting aneurysm; (2) in the renal artery wall, congenital stenosis ("fibrous intimal proliferation"), atherosclerosis, aneurysm of the renal artery, (with thrombosis), Buerger's disease, polyarteritis nodosa; (3) in the lumen, thrombosis (superimposed on degenerative changes in the wall) or embolism; (4) outside the vessel, pressure from a retroperitoneal tumour, or perhaps kinking and torsion of the renal pedicle in nephroptosis.

The resulting renal ischemia is interesting because of the several forms it may take. In cases in which severe hypertension has been relieved by nephrectomy, the kidney has shown (a) no significant defect, (b) localized patches of tubular atrophy, or (c) generalized severe tubular atrophy. The importance of this observation is that since there may be no significant pathological change in a kidney which is responsible for severe hypertension there may also be no functional alterations as detected by our usual tests of renal function.

PATHOGENESIS:

Goldblatt's original experiments were done on dogs in which he produced permanent hypertension by partial occlusion of both renal arteries or complete occlusion of one renal artery with a unilateral nephrectomy on the other side. Partial occlusion of one renal artery with an intact opposite kidney produced only transient hypertension in the dog. However, subsequent experimentors showed that this type of hypertension was permanent in rats and rabbits. It could run a "benign" or "accelerated" course.

In the human it has been established that partial occlusion of one or both renal arteries can produce permanent hypertension which is relieved by nephrectomy or vascular surgery. However it must not be forgotten that unilateral renal disease may co-exist with hypertension and not be the causative factor, as shown by the many failures to relieve hypertension by nephrectomy in

cases of so-called unilateral pyelonephritis.

The various renal lesions which are associated with hypertension have in common the production of a *viable, ischemic kidney tissue*. The sequence of rénin production by the ischemic kidney and its reaction with the alpha globulin (hypertensinogen) to form hypertensin (or angiotonin) is well known. Many problems remain unsolved, however. First, the source of renin. Some have found an increase in the juxtaglomerular complexes in these kidneys. Second, how "hypertensin" acts. Third, how to detect it in the blood, which would be very helpful in the diagnosis of renal hypertension.

In any case "hypertensin" acts to produce hypertension which results in changes in the vessels of the other kidney and throughout the body. These arterial lesions of hypertension may exhibit "benign" or "malignant" characteristics. Accordingly, the sequelae of hypertension may appear: cerebral hemorrhage, cardiac hypertrophy and failure, or progressive renal failure. For some reason the occlusive renal artery lesion exerts a "protective" action on the ischemic kidney and its vessels are not affected.

However, the pathogenesis of renal hypertension is not this simple. Another experiment has been done in which both kidneys have been removed and the animal kept alive by peritoneal lavage. Hypertension developed in the absence of any kidney tissue. Thus another hypothesis arose, namely that the kidney inactivates or excretes a pressor substance which is normally present in the blood. A decrease in viable kidney tissue therefore results in an increase in this pressor substance, and in hypertension.

Non-renal humoral factors have also been implicated but it is beyond the scope of this article to delve any more deeply into the pathogenesis of hypertension.

Diagnosis:

The diagnosis rests to a great extent on special tests, but history may also be helpful. The problem confronting us is which patients merit extensive investigation for renal causes of hypertension and which do not.

A positive family history is present in 75–85% of cases of essential hypertension, but its presence is certainly not enough to rule out hypertension secondary to renal disease. In cases due to renal artery disease, there is sometimes a history of a recent episode of unexplained abdominal pain (probably due to infarction) or a history of trauma to, or a recent operation on the kidney. However, in about one half of all proven cases there is no such history and no symptoms suggestive of urinary tract involvement.

Physical examination helps to rule out many of the other curable causes of hypertension such as brain tumour, Cushing's syndrome, or coarctation of the aorta, but helps little with unilateral renal disease unless a large palpable kidney or costovertebral angle tenderness is present. One other sign is helpful, if present: in patients with bilateral stenosis of the renal arteries, a loud systolic bruit may be heard over the upper abdomen and in the costo-vertebral angle.

Routine examination of blood and urine are seldom of help in diagnosis and thus we are left with the laboratory tests of renal function and other special tests to establish a diagnosis.

Tests of overall renal function are of minimal value in these cases of hypertension. They may be normal with one kidney completely non-functioning. Morever, even if the concentration tests, creatinine clearance or NPN are

abnormal, there is still a possibility that the hypertension may be curable. In other words, these tests are not sensitive enough. Just as there may be severe hypertension due to renal artery occlusive disease with little or no pathological change in the kidney, so there may be no functional alteration as indicated by these tests.

An intravenous pyelogram is a very useful and simple test to help exclude unilateral renal disease. However it may be normal in the presence of significant lesions so that it cannot be considered infallible. Likewise, retrograde pyelography is important and should be done in all cases where indicated.

Two more specialized tests remain at our disposal. The cases which should undergo one or both of these tests must be carefully selected as there is no need to subject the majority of patients with moderate hypertension to them.

The first test is that of bilateral ureteral catheterization (through a cystoscope) with collection and examination of the urine from each kidney separately. This is known as the differential sodium excretion test. If unilateral renal disease is present, the affected kidney will excrete a smaller volume of urine and less sodium in a given time interval. The criteria are: a decrease of 50% in the volume, and a decrease of 15% in the sodium concentrations of the urine excreted in a fixed time interval. Both criteria must be met since some cases of so-called unilateral pyelonephritis have a decreased volume of urine but an increased sodium concentration. Nephrectomy has not benefitted these cases.

The basis of the differential sodium excretion test is the experimental work of White who found in the dog that constriction of one renal artery led to a marked reduction in volume and sodium concentration of the urine coming from that kidney as compared to the urine collected simultaneously from the opposite normal kidney. It remained for Howard, Yendt, *et al.* to apply this test to humans.[13] The importance of this test is illustrated by the statement that unilateral function studies have rarely been normal (in relation to the other kidney) and subsequently that kidney is shown to be responsible for hypertension. In other words, this is our most sensitive test and it must be done finally to rule out unilateral renal disease when the index of suspicion is high.

The second procedure which is used on some cases is that of abdominal aortography and renal angiography. This is accomplished by introducing radio-opaque material into the aorta through a long needle inserted into the region of the lumbar spine, or by doing retrograde aortography through the femoral artery. Despite the dangers involved, these tests may be the only way of localizing a lesion of the renal artery.

The indications for these last two procedures have been stated as follows: (a) a young person with no family history or apparent cause for hypertension; (b) an unexplained disparity in size or function of the kidneys by I.V.P.; (c) older patients with essential hypertension who suddenly accelerate, especially when this follows an attack of pain in the flank.

Each case must be judged on its own merits, but these tests are being done more frequently in larger centres and more cases are being diagnosed as a result. Probably all cases of severe hypertension deserve at least differential sodium studies since the prognosis is so gloomy. We must also remember that even mild hypertension of long duration may be secondary to curable renal lesions.

Treatment

When the diagnosis is made, treatment is nephrectomy, thromboendarterectomy

or the replacement of renal vessels by arterial homografts, whichever procedure is most suitable to the cause of the hypertension.

Results of Treatment

The results of treatment of hypertension due to unilateral renal disease depend on many factors.

The most important factor is the selection of cases. Better diagnostic procedures are improving the selection so that the results are also better. The failures can be attributed to vascular changes already present in the other kidney which were not detected. Surprising as it may seem, the age of the patient, the duration of the hypertension and the retinal changes do not seem to be reliable guides for prognosis. The most important factor is evidence that one kidney is functioning well, while the other is functioning poorly as shown by differential sodium or angiographic studies.

Thompson reported a 50% cure rate when when the kidney was atrophic due to chronic pyelonephritis. More recently, Gellman reports a series of 27 cases of hypertension due to unilateral renal artery disease which were *all* relieved by surgery. He defined a cure as 12 months following operation with a blood pressure below 140/90. There seems to be no doubt that the results are best when the responsible lesion is in the renal artery and the diagnosis is well established by special techniques. Patients who seem on the verge of death from severe malignant hypertension may be restored to normal health by nephrectomy or repair of the renal vessels. While rigid criteria of cure are important in critically assessing the results of treatment, it must be remembered that a reversal of the malignant phase is often life-saving even if blood pressure is not restored to completely normal levels.

Conclusion

We have tried briefly to present the important aspects of hypertension due to unilateral renal disease. While its occurrence is infrequent in the overall incidence of hypertension, the problem is interesting because of its relation to fundamental experiments, and important because the removal of a kidney (or renal vascular lesion) causing hypertension may be life-saving and may bring about the return of blood pressure to normal levels. The problem is one of diagnosis and the newer techniques of differential sodium excretion and renal angiography have been outlined.

Acknowledgement

I would like to express my appreciation to Dr. E. Yendt of the Toronto General Hospital for his constructive criticism of this article.

Bibliography

1. Allen, A. C. The Kidney.
2. Bell, R. T. Renal Diseases.
3. Dexter, et al. Renal Hypertension.
4. Goldblatt, H. Excerpta Medica, Gen. Path. Anat., II, 4, April 1958.
5. Smith, H. W. J. Urol., 76:685, 1956.
6. Sweeney, J. S. and Pace, J. M. Ann. Int. Med., 29:370, 1948.
7. Poutasse, E. F. J.A.M.A., 161:419, 1956.
8. Poutasse, E. F., Duston, H. P. J.A.M.A., 165:521, 1957.
9. Gellman, D. D. Quart. J. Med., XVIII, 105, 1958.
10. Langley, G. J. and Pratt, R. Quart. J. Med., N.S. 16:143.
11. Pratt, R. Quart. J. Med., N.S. 16:111.
12. Laforet, E. G. Ann. Int. Med., 382:667, 1953.
13. Howard, Boothrong, Gould and Yendt. Bull. Johns Hopkins Hosp., 94:51, 1954.
14. Yendt. Personal communication.

THE MIND, THE PATHWAY, AND THE BODY

H. NEWTON, 5T9

ONE of the most perplexing problems that the medical student, and indeed most of the profession confronts, is a working knowledge of the human mind. We wish to know why some minds are healthy and others are not. We want to know about those peculiar body symptoms that we label psychosomatic. More than this, we want to know how these intricate disturbances of mind and body come about, and why they should occur.

The purpose of this paper is to describe a working hypothesis interrelating the dynamics of the intra-psyche, the mechanism of the nervous system, the manifestations in the body, and the psycho-neural pathway which may be involved, and to explain how this whole interrelated unit may be affected by the stress of living. The subject is highly complex, and much remains unknown. Certain facts, however, are accepted because they have been substantiated clinically and experimentally. A very basic knowledge of the subject is attainable by understanding the functions of the nervous system, and the alteration upon those functions, of stress.

A brief description of the functions of the pertinent cortical areas follows:

1. *The motor area* subserves the function of voluntary muscular movement and acts via the pyramidal pathway. Co-ordinated movement or skilled action is carried out by the extrapyramidal tract.

2. *Prefrontal lobe* receives the primary sensations and recognizes and interprets them. Crude impulses are received at the centrencephalic system (thalamus and hypothalamus) and relayed for high level functional interpretation.

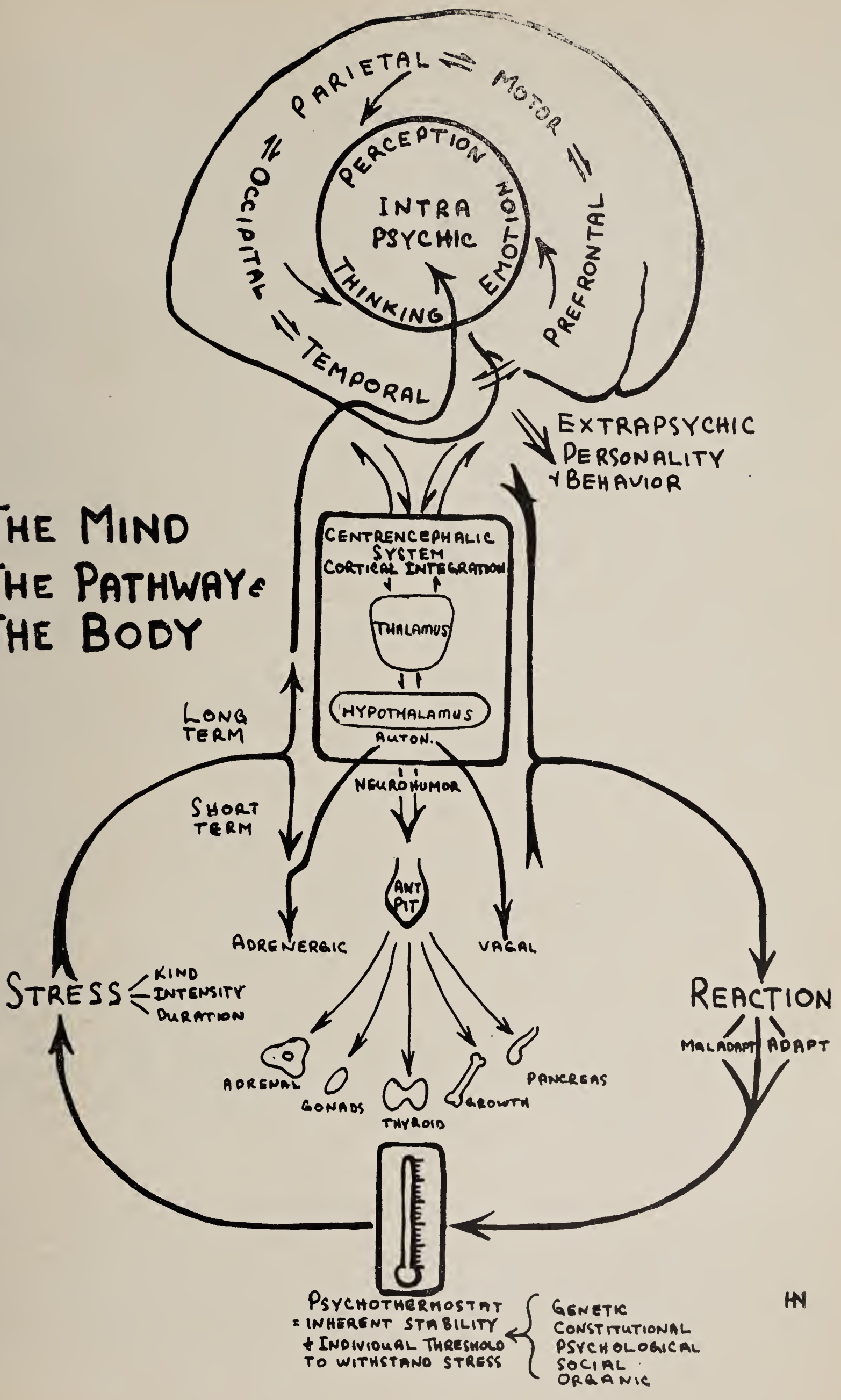
3. *The Temporal Lobe* subserves the special senses. The auditory and olfactory areas are located here. Equilibrium and memory are centered in this lobe. Dreams, those fantastic patterns of garbled memories, may be localized in the temporal lobe, but more likely are a general cortical function. Auditory sensation is analysed and interpreted into more complex perceptions in the auditory psychic area.

4. *The Occipital Lobe* is the visual area which interprets and integrates the visual sensations. Visual hallucinations arise from this lobe.

5. *The Prefrontal Lobe.* Stimulation of this area results in an autonomic response, emotional feeling, and visceral sensation. This lobe is considered a projection area for the hypothalamus, and extensive subcortical and cortical connections are present. Removal of the frontal lobe has been shown to result in definite defects of character and mentality. These include lack of restraint, initiative, morality, and recent memory. Restlessness, hypermotility, flight of ideas, euphoria, tremor and anorexia also have been observed. Any of these states may be seen in disturbed individuals. Intelligence was previously ascribed to the frontal lobes, but now is considered a function of the whole integrated cortex.

A most important realization is that the cortical lobes are not distinct functional entities. Afferent and efferent paths unite the cortices, and healthy cortical function is a result of the synthesis and association of all these functions. Mental capacity, stored experience, and the very psyche itself are a result of this smooth integration of function. Penfield states that the vast network of cortical matrix subserves the higher mental functions which distinguish man from the animals. This matrix

THE MIND
THE PATHWAYS
THE BODY



HN

must constitute an essential part of the machinery of the mind.

The Intrapsyche

Very briefly, the mind or the intrapsychic phenomena are comprised of three components, *thinking*, *perception*, and *emotion*. These functions are subserved by synthesis and interpretation of the cortices. Environment can affect emotion and thinking, but not perception. Distortion of perception is related to hereditary and constitutional factors. Thus the neuroses act primarily on emotion and thought, and the psychoses act primarily on perception.

Centrencephalic System

This system is comprised of the thalamus, hypothalamus, and the neighbouring upper brain stem. The *thalamus* is related to consciousness, emotional expression, rage, and visceral sensation (nausea, hunger, and thirst). The *hypothalamus* controls the autonomic system, and body temperature, and exerts an effect on the anterior pituitary via a neurohumoral mechanism. Penfield and Jasper believe that the centrencephalic system is a cortical co-ordinating and integrating device. It controls excitatory and exhibitory effects on local cortical function. Without these effects the cortical mantle would lie dormant. This fact is the basis of the frontal lobotomy surgical procedure for several psychoneurotic states. The fibres connecting the prefrontal lobe with the subcortex (thalamus and hypothalamus) are cut. The theory is that it is better to have no path at all rather than an erratically malfunctioning one.

Anterior Pituitary and the Hormones:

Little description of function is necessary here. The anterior pituitary is controlled by a neurohumoral mechanism from the hypothalamus. The anterior pituitary in turn controls secretion of the endocrine glands. It has long been noted that the levels of thyroid hormone, ACTH, and adrenalin rise during stress, for the purpose, perhaps, of combatting it. It is known that an individual cannot withstand stress unless this elevation occurs. The exact function of these hormones in relation to stress is not precisely known. It should also be remembered that hormonal imbalance can cause psychopathology.

The Psychothermostat:

This is an imaginary term devised for the convenience of descriptive purposes. We must liken an individual to a thermostat which is set at different levels in different people. The lower the level, the less able is an individual to withstand stress. The *genetic endowment, constitutional factors, psychological factors, social* and *organic factors* are all essential in determining the level of the thermostat and therefore the inherent resistance with which the individual may combat stress.

Stress:

Stress is the trigger mechanism of mental disorders. This stress may arise from physical disease, fatigue, trauma, mental factors, race, culture, sex, endocrine or social factors. The intensity of the stress is also important in determining the type of disorder which may be precipitated. The duration of stress is also a significant factor. Certainly stress lasting over a period of years will have a more profound effect than stress enduring a few weeks.

Reaction:

For all stresses there will be a reaction. The laws of physics inform us that for every action, there is a reaction, and for each stress, strain must develop. Whether or not the individual adapts depends on his inherent resistance forces

—i.e., the setting of his psychothermostat. The intrapsychic factors (perception, emotions and thought), which are the result of personal development and adaptation, determine how well an individual is equipped to withstand stress. Thus the psychothermostat and the intrapsychic factors afford resistance to stress, and determine an individual's stand or breakdown under it. Now, where does this stress act? We have all experienced mild stress of short duration during examinations. This trial triggers off an adrenergic response by acting mainly through the hypothalamus, and precipitating us into a mild anxiety state by throwing the autonomic system into imbalance. This is the adreno-neurotic reaction described by Selye (i.e. fearfulness, restlessness, sleeplessness, bowel upset, perspiration, tachycardia, anorexia, dilated pupils and frequency). Once this short term stress is over, the response disappears.

If, however, we are faced with a stronger stress of long duration, and the resistance mechanisms are inadequate to defend us, then we may suffer a more serious reaction. If the stress continues to act, and we continue to react, then profound mental and physical changes may result. Emotions, thought, and perception may become disordered, and temporarily or permanently disrupted, causing an alteration in our mental status and personality. The body too, registers the conflict. The functions of the whole psychoneural pathway may become disrupted so that symptoms of the mind and body become apparent.

The Body

The body may be a mirror of disturbed mental processes, often presenting with the symptoms of autonomic imbalance. In some cases, actual body pathology may result. Sweating, itching, blushing and chronic hives are well known psychogenic skin manifestations of people with an unresolved conflict. Peptic ulcers, asthma, coronaries, rheumatic diseases, herpes zoster, and goitres are just a few examples of diseases that have been due at least in part to mental disfunction. We can all remember the body symptoms of examination anxiety. Old-time physicians describe people during cholera epidemics who feared getting the disease, to such a degree that they were more prone to catch it than unconcerned, emotionally stable individuals. Hysterical blindness, deafness, and paralysis are well-known body manifestations of mental conflict. Why does one patient recover from an attack of pneumonia in a week, while another patient suffers the identical condition, yet it lingers for months? A good understanding of the psychoneural pathways affords the only explanation of these bodily disturbances. These people have a temporary or permanently lowered resistance to stress, both physically and mentally. These facts, then, form the basis of psychosomatic medicine.

Personality:

Personality represents the sum total of a person's psychological attributes. It includes the dynamic interrelation of all the mental and organ machinery which has been described. In effect, personality is the exteriorization of the intrapsychic phenomena. It is the result of our innate endowment plus our reactions to the stress of environment. No two personalities are exactly alike. The apparatus of some individuals can deal with the environment more effectively than others. In health, personality represents a cohesive balance and a smooth discharge of mental energy. In disease, the personality is affected by imbalance and incohesion of psychological and body systems.

CONCLUSION AND SUMMARY:

This article has dealt with the reaction of the whole interrelated system of the mind, the psychoneural pathways, and the body manifestations to stress. The description has been brief, and perhaps too simple. The more complex analytical concepts and psychopathology of the mind have received the most cursory coverage due to their complexity.

The purpose of this paper is to present an effort to show how the whole human structure reacts to the life it lives. In mental disease, there can be no one cause of things, but rather there is a spectrum of mechanisms, varying in quality and quantity, and involving the mind, the nervous pathways, and the body.

ACKNOWLEDGEMENT

I should like to thank Dr. D. C. Cappon for reading and assisting in the preparation of this article.

NEONATAL HEPATITIS: a problem in the differential diagnosis of neonatal jaundice

J. E. MILLIGAN, 5T9

JAUNDICE occurring in the neonatal period of life, i.e. the first 28 days, is extremely common, and may be either a passing discomfort to the parent or the manifestation of a serious challenge to the life of the baby. Unfortunately the doctor has to make some decision regarding the category which the child has to be placed in; generally speaking, any jaundice which appears in the first 24 hours of life, or persists after two weeks of age, should be considered pathological and attempts to establish an accurate diagnosis should be made.

The following is a modified etiological outline of conditions which could give rise to pathological jaundice.

A. PREHEPATIC

1. Physiological jaundice of the newborn.
2. Intrinsic Hemolytic Disease (i.e. a fault in the R.B.C.)
   - (a) Spherocytosis
   - (b) Mediterranean Anemia
   - (c) Sickle Cell Anemia
3. Extrinsic Hemolytic Disease (i.e. outside the R.B.C.)
   - (a) Rh incompatibility
   - (b) ABO incompatibility
   - (c) Rare group incompatibility

B. INTRAHEPATIC

1. Sepsis
2. Syphilis
3. Toxoplasmosis
4. Herpes Simplex
5. Generalized Cytomegalic Inclusion Disease
6. Infectious Hepatitis
7. Neonatal Hepatitis
8. Galactosemia
9. Inspissated Bile Syndrome complicating Extrinsic Hemolytic Disease
10. Congenital Familial Non-hemolytic Jaundice
11. Fibrocystic Disease
12. Congenital Atresia of Intrahepatic Bile Ducts

C. POST-HEPATIC

Congenital Anomalies of Extrahepatic Biliary Tree

- (a) Atresia
- (b) Stenosis
- (c) Choledochal Cyst with Obstruction

The practitioner is thus left with what superficially appears to be rather an imposing list of conditions which he must eliminate. However, with only a few exceptions, the great majority of these can be eliminated quite simply.

A. 1. Physiological jaundice, due to a combination of liver immaturity in the first 4–5 days plus breakdown of R.B.C.s which are formed to an excess while the fetus is in utero, has usually disappeared by the 10th day although in the premature infant it may last 2 weeks; however, the total serum bilirubin rarely exceeds 10 mgms % and it usually remains under 7 mgms %. It always presents as a retention (non-obstructive) jaundice.

2. Intrinsic Hemolytic Disease also presents as a retention jaundice usually with a family history. It can be ruled out by a normal blood smear and a fragility test which is within normal limits.

3. Extrinsic Hemolytic Disease may occasionally present as an obstructive jaundice (Inspissated Bile Syndrome) although usually it is retention in type. It is ruled out by a knowledge of infant and maternal blood groups, and if necessary Coombs' tests on infant and maternal bloods.

B. 1. Sepsis can be eliminated by clinical examination along with blood and urine cultures and White Blood Cell counts if needed.

2. Syphilis is now very rarely seen. Routine prenatal serological studies should always be done on the mother and if necessary repeated on the infant and mother after delivery.

3. Toxoplasmosis is being seen more although it is still uncommon. More frequently it will present with microcephalus and microphthalmia. It can presumptively be discarded by absence of convulsions, lack of chorioretinitis, and failure of skull X-rays to show cerebral calcification.

4. Herpes Simplex has rarely been described as affecting the liver of a newborn who has acquired the virus probably during the 2nd stage of labour. It can be suspected if the mother has a history of herpes in the perineum or elsewhere; the disease is usually manifested by a widespread visceral involvement.

5. Generalized Cytomegalic Inclusion Disease will not commonly restrict itself to the liver so that other signs such as chorioretinitis, and calcification in the lateral ventricles of the brain can usually be found. Inclusion bodies can be seen in centrifuged urine sediment and gastric washings.

6. Infectious Hepatitis, until a few years ago, was rarely if ever incriminated as a cause of jaundice in infants under 2 years of age; other studies showed that disease in the infant did not occur even when the mother had infectious hepatitis during pregnancy.[1, 2, 3] However, in 1955, an epidemic in an orphanage was studied in which 36 children under 3 years of age were shown, by virus studies done on feces and oral transmission to volunteers, to have contracted infectious hepatitis;[4] of the children involved, four were under 5 months of age. The majority of patients presented with anorexia, loose stools and fever, while only one had clinical jaundice. In 100% of cases, the Thymol Turbidity test was abnormal and other liver function tests were abnormal in over 75% of cases. No deaths were reported. The above clinical and laboratory findings are very distinct and different from the picture seen in neonatal hepatitis, as shown later. Unfortunately, infectious hepatitis cannot definitely be proven or disproven with our present knowledge of virology.

7. Neonatal Hepatitis—see below.

8. Galactosemia can be presumptively ruled out by a negative Benedict test of the urine if the patient is on a normal milk diet. There are also specific tests

for individual sugars which can be used if sugar is found in the urine.

9. Inspissated Bile Syndrome was eliminated with the extrinsic hemolytic diseases.

10. Congenital Familial Non-hemolytic Jaundice with kernicterus is a rare disease with a family history in which no evidence of excessive hemolysis can be found. It is thought that there is enzymatic deficiency in the liver which prevents the conversion of bilirubin A to bilirubin B. There is no histopathology in the liver.

11. Fibrocystic disease—very rarely blockage of the biliary system occurs in this disease. It can be suspected by signs of meconium ileus and can be eliminated by a Finger Sweat Test.

Even after the above investigations have been carried out, a large percentage of patients—probably exceeded in number only by those who have physioiogical jaundice—still remain undiagnosed. As well as being jaundiced, over one half of these have acholic stools and dark urine, most have hepatomegaly and often some splenomegaly.

Until 1952, this remaining group of infants was considered to have some obstructive element in the intra or extrahepatic biliary tree; however, at this time, Craig and Landing described a fairly consistent pathological picture which occurred in a number of these infants in whom no extrahepatic biliary obstruction was found.[5] In the liver there was a preservation of the general architecture with no signs of regenerative nodules and no dilatation of the bile ducts. The distortion of the liver cell cord pattern was extreme with a great variation in liver cell size; there were many multinucleated giant cells, with an average of 6–9 nuclei. They were usually 4–5 times the size of normal liver cells and showed some signs of degenerative change. Frequently there were sinusoidal collections of erythropoietic tissue. They suggested that this picture was one of a viral hepatitis which they called "Neonatal Hepatitis".

In 1952 also, another report described 30 out of 156 cases of obstructive jaundice in the newborn as "Inspissated Bile Syndrome of Unknown Etiology"[6] which in retrospect was decided to be identical[7] with that described by Craig and Landing.

It was recognized right from the beginning that one of the major problems in this disease was the striking similarity between it and malformations of the biliary tree both clinically and in laboratory studies. The onset of jaundice in both is relatively early being in the first 2 weeks in 84% of biliary atresias and 53% of the neonatal hepatitis group.[8] The majority of both groups have acholic stools and dark urine containing bilirubin but no urobilinogen; however, in Norris and Hays' series[8] 5 out of 52 biliary atresias had one or more pigment stools in the first two weeks of life; it is probable that these five had either intrahepatic atresia, which is usually incomplete, or extrahepatic stenosis, for extrahepatic atresia is always complete. In their group with neonatal hepatitis, one third had continuously acholic stools, one third were initially acholic but later positive for urobilin and one third were continuously slightly pigmented. Hepatomegaly was present in most cases of both groups while splenomegaly, although not constant, was commonly present, slightly more often in those with neonatal hepatitis.

The liver function tests which one would expect to be of so much aid in differentiating the two conditions, are usually equivocal. The Thymol turbidity, thymol flocculation, and cephalin cholesterol flocculation tests are usually negative, both have a high alkaline phosphatase, the prothombin time is usually normal, and the serum proteins and

serum cholesterol are not significantly different in the two diseases.[9] It has been suggested that biweekly total serum bilirubins showed distinctive differences[9] in that those with biliary atresia showed a slow progressive rise whereas there was a fluctuating level or downward trend in hepatitis; studies over a period of 24 weeks by Norris tended to support this general trend.[8] However, the individual cases did show variations; this discrepancy between statistical average and individual cases was strongly pointed out by Clatworthy in whose 23 cases of obstructive jaundice, 8 showed just such a steady fluctuation or a downward trend—3 were later proved to have biliary atresia and 4 had neonatal hepatitis, while 2 others which showed a rising trend were later proved to have neonatal hepatitis.[10]

Earlier it was also hoped that cortisone might have a useful diagnostic as well as therapeutic effect by acting as a cholagogue;[7] however, Deforges *et al.* have since shown that there is "no effect on serum bilirubin levels beyond the baseline control values".[11] The same has been shown to be the case for other cholagogues as well.

There are essentially two main reasons for wanting to be able to distinguish between atresia and hepatitis. The first has to do with the poor prognosis in untreated biliary atresia. In one study on 98 children with cirrhosis, it was found that 54 were due to biliary obstruction.[12] In another series, the majority of tests for hepatocellular damage due to progressive and irreversible biliary cirrhosis became positive by four months of age in children with atresia; in fact, 38% were positive by the end of the second month of life.[8] In all intrahepatic cases which are inoperable, the operability is judged to be anywhere from 16%[9] to 22%;[13] a not insignificant number of lives to salvage from cirrhosis with ascites, liver failure, and bleeding varices. However, they must be operated on by the eighth week of life, and indeed Clatworthy suggests the fourth week of life as the ideal time, or else changes which may be fatal have already occurred in the liver.

In the early years, the above argument was partially recognized, and so during 1952–1954 laparatomy was carried out with exploration and dissection out of the biliary tree to exclude atresia. However, it was found that such traumatic procedures worsened the prognosis of neonatal hepatitis.[4, 7] In cases untreated by surgery, 71% had recovered without sequelae by about 2 years of age, 22% had died, and 7% had recovered with cirrhosis. This is the second main reason why it was hoped that some means could be found to distinguish hepatitis from atresia. Later authors, while agreeing that extensive procedures at laparotomy may be harmful, feel that if the surgery, done under local anaesthetic or cyclopropane anaesthesia, is limited to getting a piece of liver for permanent pathological section (unfortunately a frozen section is not reliable,[8] nor is needle biopsy) and injecting only an easily found gallbladder with diodrast, then no harm will be done and the diagnosis can be made.[10] Indeed they feel that such a procedure, which may last only 30 minutes, is the only way to make a diagnosis. The permanent pathological section also enables one to diagnose the inoperable cases of intrahepatic atresia.

Other centres feel that if no bilirubin and urobilin shows in the stool then diagnostic laparotomy should be done; this would thus be on one third to half of those with hepatitis and all of those with extrahepatic atresia. However, if some bilirubin does present in the stool, then operation is postponed; one must beware that this is not bilirubin which may be in gastrointestinal juices from high blood levels and thus would rub

off onto the outside of the stool as it passed. In this group who are not operated on would be half of those with hepatitis as well as those with incomplete extrahepatic stenosis and intrahepatic atresia. It would seem that this philosophy provides the best treatment for the greatest number, although those with incomplete extrahepatic stenosis and some of those with hepatitis are not receiving the most favourable treatment.

Since the suggestion, at the onset of investigation of neonatal hepatitis, that the pathological picture seemed to be one of a viral hepatitis, there has been much speculation as to the possibility of causation by the virus of infectious hepatitis or that of homologous serum jaundice. As was pointed out earlier, the virus of infectious hepatitis seems to have been quite effectively ruled out; [7, 1, 41, 2, 3] however, virus B of homologous serum jaundice has always been a strong possibility. Stokes first suggested that the virus B was transferred transplacentally by the mother to the infant. He suggested that she was an asymptomatic carrier,[15, 16] i.e. an individual who had had a subclinical infection, and thus no history of jaundice, and usually had no signs of liver damage. To support this he cites one case in which he was able to transfer hepatitis virus from one affected infant to two out of five volunteers and from the mother to three out of another five volunteers.[16] This theory has also been supported by Scott *et al.* who reported a family in which the first, fourth, and fifth child all suffered from neonatal hepatitis;[17] however, the transfer of virus to volunteers has never been substantiated by other workers. Those favouring this theory also feel there must be some type of rising and falling viremia to explain the fact that the disease is not transferred to all the siblings. In a work on 22 adults who were known carriers of the virus B, of whom only 6 had abnormal liver function tests, volunteers were used for injection transfer to study the idea of a transient viremia; of the 60 men given injections only 21 developed clinical and/or lab signs of a hepatitis—4 had lab signs only.[18] This report could certainly be taken for support of a transient viremia; or if the viremia were constant, then it could mean some develop a subclinical and sublaboratory infection. A third possibility could be that there is an individual susceptibility-resistance factor involved so that even under identical conditions of contact only certain ones involved are susceptible enough to develop the disease. Any or all of these theories would tend to support a random transplacental infection as suggested by Stokes.

In 1955, Bowden and Donahue suggested that the pathological picture might not be specific to any one disease but rather the result of unruly liver cell degeneration following non-specific liver cell damage.[19] This has found some support by Weller *et al.* who found what they described as a typical pathological picture of neonatal hepatitis in two cases in which they were able to obtain intranuclear inclusion producing agents; in one case, urine contained bodies similar to those found in cytomegalic inclusion disease.[20]

The most recent contribution to the etiological knowledge was presented in 1958 by Hsia and Gellis *et al.* when on a study of 59 families in which one child was born with hepatitis, it was found that of 61 siblings only 50 were normal while eleven others had neonatal hepatitis; yet, in a control series of 39 families in which one child had biliary atresia, none of the 40 siblings had neonatal hepatitis. The difference between the two groups is statistically highly significant. This they felt showed a good fit for an autosomal recessive mode of genetic inheritance, but admitted it did not prove that this actually was in inherited disease.[21]

Summary

An outline of the differential diagnosis of neonatal jaundice has been given with some of the main differentiating points between the main causes. Attention has been focused on the fact that even after clinical and laboratory exclusion there is a moderately large number of cases still remaining undiagnosed. They present usually in good health and well nourished but with jaundice, usually have acholic stools and dark urine, moderate hepatomegaly, and often some splenomegaly with a high direct and indirect serum Van den Bergh but normal liver function tests. It is suggested that the majority of these diagnostic problems are either biliary obstruction due to extrahepatic atresia or the syndrome of neonatal hepatitis.

It has also been stressed that diagnosis by the eighth week is imperative so that proper surgical treatment in the cases of biliary atresia can be instituted before irreversible damage to the liver occurs. Two main schools of thought in regards to methods of diagnosis have been put forward and the three main etiological concepts of transplacental homologous serum jaundice, non-specific liver damage, and recessive genetic inheritance of neonatal hepatitis have been reviewed.

Acknowledgement

My sincerest thanks are extended to Dr. A. Sass-Kortsak whose unselfish devotion of time and stimulating store of knowledge made the writing of this article possible.

Bibliography

1. Journal of Pediatrics, 1952, 41; 13. Hsia, Taylor, Gellis.
2. Journal of Pediatrics, 1952, 41; 13. Hsia, Taylor, Gellis.
3. Journal Mount Sinai Hospital, 1947, 14; 222. Zondek, Bromberg.
4. Pediatric Clinics of North America, May 1955, Vol. 2; No. 2, Gellis, Hsia.
5. A.M.A. Archives of Pathology, 1952, 54; 321. Craig, Landing.
6. Pediatrics, 1952, 10; 243. Hsia, Patterson, Allen, Diamond, Gellis.
7. A.M.A. American Journal Diseases of Children, 1954, 88; 285. Gellis, Craig, Hsia.
8. American Journal of Surgery, 1957, 94; 321. Norris, Hays.
9. Pediatrics, 1955, Vol. 15, No. 2. Kiesewetter, Koop, Farquhar.
10. Surgical Clinics of North America, Dec. 1956, Vol. 36, No. 6. Clatworthy, McDonald.
11. A.M.A. Journal of Diseases of Children, 1956, 91; 126. Desforges, Villadolid.
12. A.M.A. Amer. J. Dis. of Children, 1955, 90;299. Craig, Gellis, Hsia.
13. Pediatrics, 1956, 18; 5. Myers, Bagenstoss, Logan, Hallenbeck.
14. A.M.A. Amer. J. Dis. of Children, 1955, 89; 701. Capps, Bennett, Mills, Ettinger, Drake, Stokes.
15. A.M.A. Amer. J. Dis. of Children, 1951, 82; 213. Stokes, Wolman, Blanchard, Farquhar.
16. J.A.M.A. 1954, 154; 1059. Stokes et al.
17. Pediatrics, 1954, 13; 447. Scott, Wilkins, Kesseler.
18. J.A.M.A. 1954, 154; 1066. Neefe, Norris, Reinhold, Mitchell, Howell.
19. Amer. J. of Med. Sciences, 1955, Vol. 230, No. 3. Bowden, Donahue.
20. Proceedings of the Soc. for Exper. Biol. and Med. 1957, 94; 4. Weller, Maconley, Craig, Wirth.
21. A.M.A. Amer. J. Dis. of Children 1958, 95; 485. Hsia, Boggs, Driscoll, Gellis.

THE ORAL HYPOGLYCEMIC AGENTS

J. E. HARRIS, 5T9

Historical Note:

AFTER the discovery of insulin and its clinical application to the problem of diabetes mellitus, investigators throughout the world attempted to develop an agent which would effectively reproduce the effects of insulin, but, unlike insulin, would be suited for oral administration. The benefits of such an oral hypoglycemic agent were obvious but the attempts to

develop it proved at first to be largely unsuccessful. The insulin substitute sought for would have to meet the following basic criteria: (a) it should provide the action of insulin when taken orally; (b) it should not irritate the G.I. tract or have unduly toxic side effects even after prolonged administration. The "perfect agent" would, in addition, have a controlled release so that it could be activated by a rise in blood sugar, being deactivated when the blood sugar fell to within normal limits; and prevent degenerative changes.

At first, attempts were made to protect insulin against the acid and tryptic digestion of G.I. secretions. These attempts were not successful.

Attention was drawn by some workers to the possibility that insulin-like substances might be found wherever carbohydrates underwent synthesis or breakdown whether in vertebrates, lower organisms or plants. A wide variety of plants, yeasts, and microorganisms were extracted and indeed a few of these extracts such as the glucokinin of yeast, blueberry extract and amellin did appear to have some hypoglycemic action. None, however, were able to stand the test of a controlled study; none were as effective as insulin and most showed severe toxic side reactions.

The study of the extracts was largely set aside as attention turned to the consideration of an almost infinite host of organic and inorganic compounds. Steroids, sulphur and nitrogen containing drugs, quinones, vitamins and metals were investigated by the score and discarded. Some few suggested possible hypoglycemic action but hardly any were considered seriously for clinical trials. Of those that were, two deserve at least brief mention. Frank in Breslau synthesized Synthalin and suggested its use as an insulin substitute. It did demonstrate hypoglycemic properties but its marked toxic effects on the liver and kidney interdicted its use. Synthalin was of some value though, since it introduced researchers to the hypoglycemic action of guanidine and this action is now undergoing intensive investigation. Antazoline hydrochloride was one of a group of antihistaminic substances found to possess hypoglycemic activity. This activity was small even with large doses, thus limiting for a time at least, its clinical application. Study of the antihistaminics and related compounds continues.

At various times in the insulin substitute search attempts were made to apply the accumulating knowledge about carbohydrate metabolism to the problem. As examples of this, one may cite the unsuccessful attempts to introduce into the diet other sugars or intermediary glucose breakdown products for glucose itself. At present this line of investigation is by and large confined to attempts to discover substances which will inhibit the peripheral inactivation or destruction of insulin in order to enhance the action of endogenous insulin or to delay its inactivation.

Perhaps the single most significant development recently in the search for the insulin substitute came in 1942 in occupied France. Janbon, while studying the use of the isopropylthiodiazole derivative of sulphanilamide in typhoid fever, found that it produced a severe prolonged and occasionally fatal hypoglycemia. Loubatières, a physiologist at the University of Montpellier, began an intensive study of the compound. He found that the sulphonamide blood levels were proportional to the degree of hypoglycemia and suggested that the compound exerted its hypoglycemic action by stimulating the production or secretion of insulin in the islets of Langerhans. When his work became known it was widely confirmed and

investigators were alerted to the possibility of hypoglycemic properties in other sulphonamides.

In the early 1950's a research group in Germany looking for soluble sulphonamides discovered the hypoglycemic action of BZ-55 or carbutamide 1-butyl-3-p-sulphanylurea. It appeared at first to be a satisfactory oral agent free of overt toxic reactions. Extensive clinical trials were conducted and the drug appeared to give a good therapeutic result in 50 to 90% of the cases in which it was tried, provided that the cases were confined to "pyknic, obese adults with a fairly stable diabetes of short duration". However, by the time the study of the drug had involved some ten thousand cases, an incidence of side effects of about 5% was discovered. These ranged from mild skin rashes to agranulocytosis, exfoliative dermatitis and marked goitrogenic effects. Cases of apparent liver damage and interstitial myocarditis were also reported. Because of these fatal toxic reactions which the drug occasionally produced, it was withdrawn from clinical use.

The brief introduction of carbutamide stimulated work to develop a clinically safe sulphonamide-hypoglycemic agent utilizing the sulphonylurea part of the carbutamide molecule, the part responsible for its hypoglycemic action. This work led to the synthesis of a large number of new sulphonylurea derivatives. Of these the most promising and effective are tolbutamide and chlorpropamide. Both of these drugs are currently being used for oral therapy, as insulin substitutes, in selected cases of diabetes mellitus and their use is undergoing an intensive study. A third and possibly equally effective sulphonylurea, methexamide, is currently undergoing preliminary laboratory study prior to being subjected to clinical investigation.

From Frank's original work with Synthalin, has come the recent synthesis of a number of hypoglycemic biguanides whose site of action differs from that of the sulphonylureas. These too are presently undergoing extensive clinical and laboratory investigation.

Mechanism of Action:

1. sulphonylureas:

Most workers now generally subscribe to the "pancreotropic hypothesis" of sulphonylurea action, albeit some do so with reservations. According to this hypothesis, the sulphonylureas act by stimulating the beta cells of the pancreas to secrete increased amounts of insulin. (There is evidence to suggest also that the chronic administration of the sulphonylureas may give rise to the formation of new beta cells. This is probably a temporary effect.) The insulin secreted passes into the portal vein and thence directly to the liver where it exerts its first and possibly only action. The liver, under the influence of the insulin, decreases its output of glucose into the blood by (a) increasing the storage of glycogen; (b) reducing gluconeogenesis, or (c) stimulating lipogenesis from carbohydrate. Hypoglycemia results. There is some evidence that insulin, released due to sulphonylurea stimulation of beta cells, on leaving the liver, affects in addition, the peripheral utilization of carbohydrate. However this evidence is disputed. Some workers have postulated that insulin secreted into the portal vein and passing directly into the liver may have a metabolic effect different from insulin administered peripherally. Other workers suggest that the insulin first passing through the liver in response to sulphonylurea stimulation will have its peripheral action removed or at least reduced to the point where it defies quantitative estimation. Although the great mass of available evidence sup-

ports the "pancreotropic hypothesis"; beta cell stimulation alone does not satisfactorily explain sulphonylurea action. That this is the case is suggested by the following observations: (a) the sulphonylureas are ineffective in diabetic acidosis where insulin ordinarily exerts its greatest effect; (b) hypophysectomy does not increase their effect; (c) the sulphonylureas still exert a hypoglycemic action in the hepatectomized animal presumably by the promotion of peripheral utilization. Additional mechanisms such as the inhibition of insulinase of delaying the breakdown of insulin or interfering directly with hepatic glycogenolysis through action on hepatic enzymes have therefore been suggested. The definitive solution remains to be found.

2. BIGUANIDES:

There is even less information available about the site and mechanism of action of the biguanides. What little is known suggests that they decrease hepatic glucose output and increase muscle glucose uptake. In addition they will decrease hepatic glycogen and increase muscle glycolysis. (Some recent experimental work indicates that the anaerobic glycolysis which may produce the hypoglycemic effect occurs as the result of the suppressing of oxidative reactions.) The biguanides are active in the absence of the liver. They may have some effect in delaying or reversing the degenerative changes often accompanying diabetes. This has been suggested by a report of the restoration of normal venular tone in abnormally dilated venules of the bulbar conjunctiva in juvenile diabetics treated with phenethylbiguanide.

INDICATIONS:

1. SULPHONYLUREAS:

These drugs are most effective in elderly, obese patients suffering from a mild, stable, maturity-onset diabetes of relatively short duration which cannot be controlled by diet alone. Those over 45 and requiring less than 40 units of insulin daily are most amenable to therapy. The great majority between 20 and 40 are refractory. The sulphonylureas are contraindicated in (a) juvenile diabetics; (b) diabetes following pancreatectomy or pancreatic disease; (c) diabetics during pregnancy; (d) diabetes with associated renal lesions; (e) diabetes complicated by acute infection and/or ketosis; (f) patients who do not need insulin to control their diabetes; and (g) unstable or brittle diabetics. Since chlorpropamide has been reported to show a somewhat greater hypoglycemic effect than tolbutamide and to be significantly more effective than it on daily administration, a trial of chlorpropamide is often indicated in patients who become refractory to tolbutamide or in whom control of the diabetic conditions is incomplete with tolbutamide.

2. BIGUANIDES:

The biguanides have been found to be effective in varying percentages of not only the stable adult type, but also in the juvenile and the unstable adult types.

They have not been found to be effective in long standing diabetes with degenerative vascular changes. Many cases of brittle diabetes with severe, difficult-to-control reactions have become better regulated when a biguanide was employed along with a decreased dose of insulin. The biguanides have given, in some cases, adequate control of diabetes in instances where both tolbutamide and chlorpropamide have failed. Recently there have been reports of the successful treatment of tolbutamide-failure diabetes with a combination of phenethylbiguanide with tolbutamide or chlorpropamide. The bigua-

nides are effective in some cases of both juvenile and adult diabetes, labile and stable, but it is difficult to predict in any given case whether they will give a satisfactory response. In addition there are important limitations to their use which will be discussed in the consideration of toxic effects.

Much information, then, has been accumulated about the indications for both types of hypoglycemic agents, but well-defined areas for their application still remain to be delineated.

TOXICITY:

1. SULPHYLUREAS:

(a) *Tolbutamide*: The incidence of toxicity in tolbutamide therapy has been variously reported as ranging from 3% to 9%. Toxic and other side reactions which have been noted are: mild skin disturbances of an allergic nature, a marked tendency to weight gain, G. I. disturbances, headaches, weakness and paraesthesiae. Some cases of leukopenia have been observed but there has not been any severe depression of granulocytes. Many of the milder reactions clear even though drug therapy is continued. No liver damage has been reported. Marked hypoglycemic reactions have occasionally been seen. Clinicians should be aware that tolbutamide will produce a flocculent precipitate when the ordinary tests for albumin are performed on urine due to the excretion of carboxylated products of tolbutamide. This may be interpreted incorrectly as a positive test for albumin. The Albutest tablet is not effective.

(b) *Chlorpropamide*: Nausea, vomiting, epigastric distress, dizziness, weakness and headache have been reported with the higher dosages of chlorpropamide. Decreasing the dosage will often give some relief from these symptoms. Allergic skin reactions may occur but will disappear on withdrawal of the drug. Severe prolonged hypoglycemia has been reported as has jaundice of the intracanalicular biliary stasis type. The latter will completely disappear on cessation of therapy. No impairment of renal function has been observed. Patients may occasionally demonstrate mild leukopenia, eosinophilia, lymphocytosis and transient thrombocytopenia. These will often clear even though therapy be continued.

2. BIGUANIDES:

The biguanides exert no untoward effects upon liver or bone marrow function. No significantly severe hypoglycemia has been found. There is an insignificant increase in thyroid I^{131} uptake but no change in serum PBI or cholesterol levels. Within 24 to 48 hours after commencing therapy, severe anorexia, nausea, vomiting and diarrhoea have been noted in varying percentages of patients. Extreme degrees of lassitude have also been reported. With the biguanides the dose required appears to vary with the severity of the diabetic state. When an efficacious response is obtained it bears, usually, a close relationship to the dosage level. This is not the case with the sulphonylureas where little increase in therapeutic effect is obtained by increasing the dosage. Unfortunately though, increased dosages of the biguanides are poorly tolerated, giving rise to the symptoms above noted. Since in many cases it is difficult to increase the dosage to an effective level without resulting in markedly severe G.I. disturbances, the biguanides have a narrow therapeutic range and a resultingly limited clinical application. The G.I. disturbances are easily reversed when therapy is stopped.

DOSAGES:

1. SULPHONYLUREAS:

Initial dosage of tolbutamide will range from one to three gm. depending on the severity of the diabetic state and

the insulin requirement. The daily maintenance dose is 0.5 to 1 gm. No significant difference has been found between single or divided dosage.

With chlorpropamide the patient is begun on a dosage level of 250 to 500 mgm. The lower range is reserved for older patients who appear to be more sensitive to the hypoglycemic action of chlorpropamide. Maintenance dosages will range from 100 mgm. to 1 gm. (but no more!), the majority being well controlled by 250 to 500 mgm. daily. A single dosage after breakfast is recommended, but mild G. I. disturbance is an indication for divided dosage.

In beginning treatment with the sulphonylureas, insulin dosage is reduced by 20 to 50% daily in severe diabetics with a high insulin requirement, but may be stopped abruptly with stable, mild diabetics with very low insulin requirements. Alcohol in sulphonylurea therapy is contraindicated since occasionally a disulphiram-like reaction has been noted. Therapy should be stopped and insulin again given if any of the following result: toxic reactions, no clinical improvement, ketonuria, persistent hyperglycemia and increasing glycosuria. There should be close supervision during the period of insulin withdrawal and during the first 1 to 2 months of therapy. Hospitalization may occasionally be warranted during the transfer period from insulin to the sulphonylureas. Hypoglycemia should be carefully watched for and in the case of intercurrent complications and infection, insulin therapy should be resumed.

A short-term test with the sulphonylureas is useful but not conclusive in predicting the eventual response to them. Many patients will demonstrate a favourable response to the sulphonylureas but then "relapse" and require a return to insulin therapy. This may be the result of the sulphonylureas having overstimulated and finally exhausted the beta cells. Chlorpropamide is often effective in patients who have become refractory to tolbutamide. When insulin therapy is of necessity resumed due to failure with the hypoglycemic agents, the dose requirement is no higher than before.

2. BIGUANIDES:

Phenethylbiguanide is given in dosages ranging from 100 to 300 mgm. daily, in at least two doses. Because of the marked G. I. disturbances which increased dosages occasion, dosages should be increased, when necessary, slowly and with caution. G. I. distress may be overcome at least in part, by giving the drug after meals instead of before. When a dosage of over 100 mgm. is required, the incidence of G. I. side effects is about 40%. The drug, in varying dosages, usually short of its maximum effective dose, may be combined with the sulphonylureas or insulin as previously mentioned.

SUMMARY:

A brief history of the oral hypoglycemic agents has been given. Their mechanism of action, indications, toxicity and dosages have been discussed. It is concluded that when properly applied they will have a basic and useful place in the therapy of diabetes mellitus. The long-term consequences remain to be assessed.

ACKNOWLEDGEMENTS

The author wishes to express his thanks to Dr. D. W. Clarke for his very kind advice and assistance. The technical help of Mr. Max Teska and Mrs. George Harris is also gratefully acknowledged.

BIBLIOGRAPHY

1. BEASER, N. Eng. J. Med. 259: 1207–1220, 1958.
2. BEASER, N. Eng. J. Med. 259: 571–573, 1958.
3. "Texas symposium on Phenethylbiguanide", Feb. 1959.
4. C. M. A. J., 74: 15, June 1956.

5. Annals N. Y. Academy of Sci., 71, P. 1–292.
6. Weinhouse et al. J. Clin. Invest.: 37: 631. 1958.
7. Krall, et al. Diab. Vol. 7, 468–477, 1958.
8. Tornow, et al. Diab., Vol. 8: 1–6, 1959.
9. Loubatières Diab., 6:408–417, 1957.
10. Vaughan. Diab., 6: 16–17, 1957.
11. Ricketts, et al. Diab., 6: 91–93, 1957.
12. Goldner. Diab., 6: 259–262, 1957.

HYPOFUNCTION OF THE ADRENAL CORTEX IN INFANCY*

J. HOFFMAN, 5T9

THE subject of adrenocortical hypofunction is a large one and covers two groups of clinical conditions—those in which it is the main entity, and those in which it is only one of the features of some other disease. A classification of the various types of disorder will provide some perspective on the topic.

Adrenocortical insufficiency may be acute or chronic, and partial (i.e., involving only mineralo- or gluco-corticoids) or complete (deficient in all three types of steroid). Acute types, or Addisonian crises, may be due to congenital hypoplasia; hemorrhage into the adrenals, as in trauma or diathesis; meningococcal meningitis, diphtheria, and other conditions in which the Waterhouse-Friderichsen syndrome occurs; enzyme defects in the adrenogenital syndrome; developmental defects as in transient adrenal insufficiency and some cases of spontaneous hypoglycemia of infancy; and lastly, iatrogenic states such as bilateral adrenalectomy for Cushing's disease, removal of a unilateral functioning adenoma of the cortex, and sudden cessation of cortisone therapy. Chronic adrenal insufficiency includes Addison's disease, which is tuberculous half of the time and nontuberculous the other half; hypopituitarism; and a questionable "constitutional" type of hypoadrenocorticism. Children usually exhibit the acute type, and adults the chronic.

*Presented to the Alpha Omega Alpha Honour Medical Society, Monday, Feb. 16, 1959.

Addison's Disease

Addison's disease is rare in children; only 59 cases were reported prior to 1946. There is no difference in sex incidence. Many more cases occur in middle life.

Let me quote part of Addison's original description. There is "a general languor and debility . . . remarkable feebleness of the heart's action . . . irritability of stomach . . . peculiar change of colour of skin. . . . The body wastes, pulse becomes smaller and weaker, and the patient gradually expires." The main clinical features are weakness, easy fatigue and weight loss, pigmentation, anorexia, nausea, vomiting and diarrhoea, hypotension, loss of body and axillary hair. These symptoms and signs occur with varying frequency: 95% of cases have pigmentation, 85% gastrointestinal symptoms, 13% hypoglycemic convulsions, and in the fatal instances 32% have dramatic episodes just prior to death; the heart size is usually decreased; hypotension is not frequent.

The presenting features are usually weakness and fatigue, pigmentation, and anorexia with nausea and vomiting. During the course of the disease, acute crises are common, often precipitated by infection or other stress, and marked by dehydration and hemoconcentration.

The characteristic pigmentation of the skin deserves some attention. It usually occurs on those areas normally exposed to sunlight, but is more significant when present on the buccal mucosa, areola,

anogenital region, and on the palms and soles and in flexor skin creases. It may take the form of freckling, enlargement of moles, or formation of new jet black spots which may be surrounded by an area of vitiligo. An increased level of MSH, (melanocyte-stimulating hormone), elaborated by the anterior pituitary gland in accord with the "push-pull" mechanism is the cause. The differentiation from other conditions with pigmentation may not be easy—for instance, racial pigmentation, sun-tan, the action of metallic compounds of arsenic, bismuth, lead and mercury, and the café au lait spots of von Recklinghausen's disease and polyostotic fibrous dysplasia.

The diagnosis of Addison's disease may easily be missed. Although not a common disease, it does endanger the life of the child who has it. If diagnosed, it can be treated. There are certain circumstances, therefore, when one should think of the disease:

(1) recurrent gastrointestinal symptoms as already mentioned;

(2) dehydration either of sudden and severe onset or persistent in nature, especially if there is little or no response to intravenous saline therapy;

(3) recurrent spontaneous hypoglycemia;

(4) a craving for salt, although this may occur without Addison's disease, and vice versa.

Any child, then, with asthenia, anorexia, weight loss, recurrent dehydration, hypoglycemia, and general debility, should be suspect.

On proceeding to various laboratory tests, one will find that:

(1) the oral glucose tolerance curve is flat;

(2) the insulin tolerance test is dangerous (it should not be done);

(3) there is hyponatremia and hypochloremia, but serum sodium and chloride may be normal if the extracellular fluid volume is decreased;

(4) an elevated potassium level is a consistent finding, and if high enough there will be characteristic electrocardiographic changes;

(5) the hematocrit, BUN, and NPN are all increased.

Procedures of more diagnostic value include:

(1) The Cutler-Power-Wilder, or salt depletion test. This is dangerous in an individual who is already unable to conserve salt, and should not be used.

(2) The Robinson-Kepler-Power, or water-loading test. In this test, the urinary excretion of an ingested water load over a *prolonged* period of time is taken to indicate a plasma level of corticosteroids inadequate for normal water retention. The exact mechanism is not understood. Two possibilities are that (a) there is a specific renal tubular defect in Addison's disease, which may be overcome by administering glucocorticoids, and (b) that some corticosteroids have a diuretic effect normally masked by the sodium-retention effect. The water-loading test is of no great danger to the patient, but the main value of the test is to rule *out* Addison's disease, i.e., when the test is negative. However, since it is not entirely reliable, it should be discarded.

(3) The ACTH (Thorn) test. This is the most specific and the safest test available. Prior to the administration of a given dose of ACTH in I.V. saline, urinary 17-hydroxy- and 17-ketosteroids are measured over two 24-hour periods, and a blood eosinophil count is done. Then 25 units of I.V. ACTH in saline are given over an 8-hour period on two successive days. This should stimulate the normal adrenal cortex to step up its production of hormone to the extent that urinary breakdown products show a 100% increase; at the same time the increased plasma level of hormone should result in a 70% decrease in eosinophil count, but this effect is more variable than that on urinary steroids.

In Addison's disease there may be a *normal* level of urinary steroids, but there is *no* rise when ACTH is given because the adrenal cortices are unable to respond. In such a case I.V. ACTH should be given for a third and fourth day, since an adrenocortical insufficiency secondary to hypopituitarism will show a delayed increase in urinary 17-hydroxy- and 17-ketosteroids.

The administration of 9-alpha-fluorohydrocortisone (1.0 mg.) prior to the test is a therapeutic measure which will improve the patient's ability to conserve salt, without altering the validity of the test by affecting urinary steroid levels very appreciably. In fact, in a patient with no endogenous steroid, an allergic reaction to ACTH may occur which can be prevented by giving fluorohydrocortisone on the days of the infusion.

Radiological diagnosis of Addison's disease is often equivocal, because calcification of the adrenals may occur in the absence of disease, and disease may be present when there is no calcification. During phases of remission the other tests described may also be of little value.

The therapy of the acute Addisonian episode must overcome the dehydration, repair the electrolyte imbalance, replace endogenous corticosteroids, maintain the blood pressure at an adequate level, and eliminate any precipitating factors such as systemic infection. The patient, then, needs the following:

(1) rapid intravenous glucose and saline infusion for at least 24 hours;

(2) hydrocortisone hemisuccinate 100 mg. I.V. stat or in a drip, for an effect lasting for 4 to 8 hours;

(3) levophed in an I.V. drip if hydrocortisone is not sufficient to bring the patient out of shock;

(4) antibiotics if indicated.

Desoxycorticosterone acetate should *not* be given along with hydrocortisone because this will enhance the danger of steroid overdosage, with edema, increased blood pressure, and even convulsions. The estimation of daily serum electrolytes and an occasional ECG will prevent this.

In the subacute stage of the disease or following an exacerbation, the child should be on a 3 to 6 Gm. salt diet and 25 to 50 mg. of cortisone acetate I.M. every 3 or 4 days. Eventually, 10 to 15 mg. of cortisone can be taken orally q. 12 h., as replacement for endogenous glucocorticoids, and DOCA 1.0 mg./day I.M. as replacement therapy for mineralocorticoids. A subcutaneous 125 mg. pellet of DOCA will provide about 0.5 mg./day for 9 to 12 months. If there are indications of increased absorption, the salt intake can be cut down. During periods of "stress" (infection, surgical procedures, etc.) the dosage of cortisone must be increased. As an alternative to DOCA, 0.5 mg. of 9-alpha-fluorohydrocortisone per day is highly effective.

Before leaving the subject of Addison's disease, I wish to leave with you a few varied thoughts on the pathogenesis of the condition. Firstly, a syndrome with familial incidence was noted in one series in 5 out of 12 cases under 10 years of age. The syndrome consisted of a triad of moniliasis, hypoparathyroidism, and adrenocortical insufficiency. It may become more frequent (with or without the moniliasis) now that it has been recognized.

Another author has considered that adrenal hypoplasia is the basis of most cases of Addison's disease.

Lastly, some work by Anderson *et al.* in England points to a similarity between Addison's disease and Hashimoto's disease of the thyroid gland. Complement-fixing antibodies are present in the circulation in Hashimoto's disease, the patient presumably being allergic to his own thyroglobulin. A few of these people simultaneously have Addison's disease, and circulating anti-adrenal antibodies have been found in their blood in addition to the anti-thyroid

antibodies. Further, in Hashimoto's struma there is marked lymphoid infiltration of the thyroid gland, and in Addison's disease there is often both local and general lymphoid hyperplasia. On these bases, the group in England suggest that the pathogenesis of both diseases is that of an auto-immune mechanism. The work is only preliminary, but it is interesting.

The Waterhouse-Friderichsen Syndrome

The Waterhouse-Friderichsen syndrome is usually thought of as a condition of massive bilateral adrenal hemorrhage due to meningococcal septicemia and resulting in rapid circulatory collapse and shock. Some would say that the diagnosis can only be made post-mortem, based on the finding of the massive adrenal hemorrhage; it is more practical, however, to consider it as a clinical syndrome. Other less frequent causes than fulminating meningococcal septicemia are diphtheria, staphylococcal and streptococcal septicemia, birth trauma occurring with breech or forceps deliveries, and thrombosis of the adrenal artery or vein.

Usually, the Waterhouse-Friderichsen syndrome is recognized by the presence of acute infection together with profound circulatory collapse. It occurs in 2 to 4% of all meningococcic cases, and 90% are under 9 years of age. It starts in a previously well child with fever, malaise, and headache, with or without vomiting, and with or without chills. Within 4 to 12 hours a widespread hemorrhagic rash develops with severe toxicity and possibly convulsions. The child rapidly becomes hypotensive, then cyanotic, and dies. Signs of meningitis may or may not be present. The disease is fatal 24 hours after the onset.

During the course of the disease there is azotemia and hypoglycemia. The serum electrolytes are normal or depressed. Pathological findings, other than those in the adrenal cortex, are acute passive congestion of the lungs, toxic degeneration of liver, kidney, myocardium and spleen, and engorgement of small vessels throughout the body. A number of factors contribute to the hemorrhage: dilatation and ischemia of capillaries (and to a lesser extent of arterioles and venules); platelet thrombi causing endothelial ischemia; thrombocytopenia consequent to the platelet thrombi; and bacterial embolization.

The severity of the disease varies directly with its duration, and, in one series of 27 cases, was correlated with the pathological changes in the adrenal glands themselves. The results of this study were as follows:

(1) There was massive bilateral adrenal hemorrhage in 4 cases. The medulla was not involved. The hemorrhage spread from the zona reticularis outwards to involve the zona glomerulosa. The hemorrhage is *not due* to loss of support of sinusoidal walls by atrophied cell cords, since tubular degeneration starts in the outer zone, whereas the worst hemorrhage is in the inner zone of the adrenal cortex. Hemorrhage into the adrenals seems more likely due, then, to a direct attack on the vascular endothelium by the organism and/or its toxins. All of this group occurred in the first 2½ years of life, and none of the infants survived longer than 24 hours with the syndrome.

(2) Patchy hemorrhagic necrosis together with tubular degeneration was noted in 10 cases. This was clinically less severe than the first group.

(3) Tubular degeneration only, was present in 9 instances. Some elaboration is necessary at this point. The cells of the adrenal cortex shrink due to a rapid depletion of lipid hormone in response to body injuries. The cell cords then separate to form pseudotubules which become filled with fluid exudate and

cellular debris. This process starts in the zona glomerulosa and moves inwards; as mentioned, it is the reverse of the hemorrhagic process. This group had relatively mild clinical manifestations.

(4) In 4 cases there were no significant adrenal lesions.

No persistent adrenal hypofunction has been noted in children who have recovered from the Waterhouse-Friderichsen syndrome, and the data available indicate that damage to the adrenals, aside from massive hemorrhage, is reversible. Normal plasma corticosteroid levels are 12 microgm./-100 ml. This may increase to 30 microgm./100 ml. in children subjected to severe stress, e.g., systemic infection, but without a Waterhouse-Friderichsen syndrome. In children with the syndrome, the adrenocortical response is adequate to provide a plasma level of only 17 microgm./100 ml. This is considerably higher than the normal value, but not sufficient to cope with the septicemia.

Development Anomalies of the Adrenal Glands

Only a few of the conditions related to the development of the adrenal glands will be mentioned. It will help to recapitulate the normal process. The intrauterine gland is mostly fetal cortex, consisting of sheets of large eosinophilic cells containing no lipid. It secretes weak androgens and a sodium retaining factor. For the first 20 weeks of gestation the gland is maintained by placental chorionic gonadotrophin, and during the latter half of gestation by L.H. (luteinizing hormone) of the fetus's own anterior pituitary gland. At birth the fetal cortex comprises 80% of the gland, and is surrounded by a rim of adult cortex, the zona fasciculata being atrophic because fetal ACTH has been suppressed by maternal placental steroids. The fetal cortex starts to degenerate and is 50% smaller at three weeks of age. The adult cortex proliferates slowly for the first four days of life, then rapidly; the medulla also grows larger.

In anencephaly, however, prenatal atrophy of the fetal cortex occurs in the second half of gestation. The usual amount of adult-type cortex may be present. It is interesting to note that the pars intermedia and pars nervosa of the pituitary gland are often absent in these anencephalics.

An entity known as transient adrenocortical insufficiency has been described, usually between the ages of 6 weeks to 4 months, and mainly in males. Clinically it resembles Addisonian crises previously described, but spontaneous recovery eventually occurs. There is apparently a deficit in mineralo- and glucocorticoid secretion, and this may be due to a failure of the adult adrenal cortical cells to start functioning well enough before all remaining maternal corticosteroids are used up. Fetal adrenals secrete mainly 19-carbon steroids, which do not promote gluconeogenesis; this leads to a hypoglycemic tendency in early life. Replacement hormone therapy should not be given unless adrenocortical insufficiency is proved, because the sodium loss that occurs may be due to a pair of kidneys still immature and unable to conserve. If cortisone is given, the observation of sodium retention followed by a diuresis upon withdrawal of the steroid still does not prove the diagnosis, since this would occur even if the child had no adrenal hypofunction. It must also be pointed out that, even where a low level of endogenous corticosteroids is demonstrated, the administration of exogenous hormone is likely to delay the maturation of the infant's adrenal cortex. Finally, not only is the management of the condition in doubt, but also its existence.

Some cases of spontaneous idiopathic

hypoglycemia of infancy respond well to ACTH therapy, but not to corticosteroids or other drugs. The pathogenesis may be that described in the previous paragraph.

No cases have been described in which there is a deficiency in androgenic corticosteroids only.

The Adrenogenital Syndrome

In this condition there is precocious puberty in the male and pseudohermaphroditism in the female, due to excessive secretion of adrenal androgens. One-quarter of these children, however, also exhibit the electrolyte imbalance characteristic of Addisonian crises, and a smaller number are hypertensive; a few have hypoglycemia.

The syndrome occurs equally often in males and females. It has a familial incidence which can be explained genetically on the basis of a recessive, mutant gene occurring in one in 128 persons; in other words, if two people who each have the gene marry, there is a ¼ chance that any one of their children will receive the homozygous combination and exhibit the disease. The overall incidence of the condition is 1:65,000.

Pathologically, there is hyperplasia of the zona reticularis, the zone that corresponds roughly with the fetal cortex and the zone that produces adrenal androgens. The zona glomerulosa which produces mineralocorticoids normally is absent in those cases with sodium loss, and hypertrophied in those cases with hypertension. In a sense, the condition simulates a normal fetal developmental stage. However, there is no ACTH in the blood of a newborn, and administration of ACTH causes an increased plasma level of corticosteroid in the newborn; in the adrenogenital case ACTH is present, and giving exogenous ACTH produces no response.

Clinically, the child is irritable, anorexic, and vomiting. There is dehydration and circulatory collapse. In a few cases there is hypertension also. The females all are pseudohermaphrodites, and the males have macrogenitosemia praecox but this may not be recognizable until near puberty.

The normal biosynthesis of hydrocortisone depends upon the hydroxylation of progesterone, in stages, at the 17, 11, and 21 Carbon atoms. The latter two steps require the presence of two enzymes normally present—11-hydroxylase and 21-hydroxylase. If 21-hydroxylase is absent, 17-OH-progesterone cannot be converted to hydrocortisone and accumulates; its degradation product is pregnanetriol, and this appears in the urine rather than the degradation product (tetrahydrocortisone) of hydrocortisone. Normally the amount of urinary tetrahydrocortisone is 50 times that of pregnanetriol.

If 11-hydroxylase is absent, then DOC and Compound S accumulate. Their degradation products pregnane—3α, 17α, 21-triol-20-one and pregnane—3α, 21-diol-20-one, respectively appear in the urine. However, no 11-OH corticosteroids, which are normally present, appear in the urine. DOC is an active metabolite, and causes hypertension. This is in addition to the Addisonian symptoms.

There is an intermediate group of cases which have adequate corticosteroid levels most of the time, but are unable to cope with stress.

The result of the deficient hydrocortisone production is excessive ACTH secretion. This results in a hyperplastic adrenal cortex which then produces more of the hydrocortisone precursors described above, and large amounts of androgens. The androgens depress FSH secretion by the anterior pituitary gland so that there is a resultant ovarian or testicular hypoplasia as the case may be. The androgens also exert their other

characteristic effects upon the body, causing pseudohermaphroditism in the female and precocious puberty in the male.

For diagnostic purposes, urinary pregnanetriol is of more value than 17-ketosteroid excretion, especially in the first year of life and in males. Urinary aldosterone may be increased as a compensatory mechanism in cases of salt-losing adrenal hyperplasia. Some authors feel that the reason for this is the secretion of a salt-losing hormone by the adrenal cortex which either prevents the action of aldosterone or causes a sodium diuresis. Other evidence in favor of this hypothesis is that administration of ACTH may precipitate a sodium diuresis in these children, and that they require higher doses of DOCA than do adults with Addison's disease.

Summary

This paper is a survey of the important types of hypoadrenocorticism in children. It has presented primarily some recent advances in pathogenesis, diagnosis and therapy.

Bibliography

1. Wilkins, Lawson: The Diagnosis and Treatment of Endocrine Disorders in Childhood and Adolescence. Ed. 3, 1957.
2. Anderson et al.: Autoantibodies in Addison's Disease. J. Lancet *2*: 1123, 1957.
3. Bongiovanni, A. M., and Eberlein, W. R.: Defective Steroidal Biogenesis in Congenital Adrenal Hyperplasia. Pediatrics *21*(4): 661, 1958.
4. Greenberg: Addison's Disease in Children. J. Pediatrics *52*, 1958.
5. Thomson, J. B., and Shapiro, J. L.: Adrenal Lesions in Acute Meningococcemia. A.M.A. Arch. Path. *63*(6): 527, 1957.
6. Nelson, J., and Goldstein, N.: Nature of Waterhouse-Friederichsen Syndrome. J.A.M.A. *146*: 1193, 1951.
7. Benirschke, K.; Bloch, E.; Hertig, A. T.: Concerning the Function of the Fetal Zone of the Human Adrenal Gland. Endocrinology *58*: 598, 1956.
8. Adrenal Cortical Metabolism of Fetus, Infant, and Child: in Pediatrics *17*: 897, 1956.
9. Malloy, B. M., and Woodruff, C. W.: Addison's Disease in Three Six-year Old Boys. A.M.A. J. Dis. Child. *95*(4): 364, 1958.
10. Laidlaw, J. C.; Reddy, W. J.; Jenkins, D.; Abu Hayder, N.; Renold, A. E.; Thorn, G. W.: Advances in the Diagnosis of Altered States of Adrenocortical Function. New Eng. J. Med. *253*: 747, 1955.
11. Hoyrup, E.: Impaired Adrenal Function as a Contributory Factor in Constitutional Asthenia. Acta Psychiat. Neur. Scand. suppl. 108: 185, 1956.

BRONCHIECTASIS

C. G. GONSALVES, 5T9

IN 1819 Laennec published the first historical description of bronchiectasis as an independent and well-defined disease. The definition of the disease can be found in its name which describes it as being an "ectasia" of a bronchus, meaning bronchial dilatation. Its incidence is roughly about 0.5 per thousand in the population.

Etiology

A great deal has been written about bronchiectasis, yet the essential cause remains a mystery. Precipitating factors are well-known, but are such factors the very basis of the disease, or must there also be present a more basic lesion such as a constitutional defect in the bronchial wall? The problem may be

elucidated by considering the hypothetical significance of certain clinical observations. It is known that the disease may occur in one lobe, in several lobes of the same lung, or that it may be bilateral. If due entirely to infection and obstruction, would not the disease, in fully developed and longstanding cases eventually involve both lungs, or at least more than one lobe, much more often than it in fact does? Consider also the fact that patients with bilateral bronchiectasis who have been treated by unilateral lobectomy and/or segmental resection do not develop new bronchiectasis due to the presence of the disease on the non-operated side nearly as often as one might expect. On the other hand, if due to a basic constitutional defect one would hardly expect to see the disease confined to the basal segments as frequently and as characteristically as one in fact does.

Before proceeding further let us consider certain physiologic principles operating in the normal bronchial system of the lungs. Essential to the integrity of the bronchial tree are those elements, namely cartilage, muscle and elastic tissue, which give the tubes strength and prevent sagging and pool-formation. On inspiration the bronchial tree dilates and on normal expiration returns to its resting state. The secretions normally elaborated by the bronchial mucosa are removed by the cilia which have been shown to beat in a rhythmic fashion away from the periphery. Ciliary action is important and is not to be underestimated. Drainage of secretions is further influenced by gravity so that secretions might more easily accumulate in certain regions of dependency such as the lower lobes, than in other regions such as the upper lobes.

In the pathogenesis of bronchial dilatation no one questions the importance of infection and obstruction. Severe, long standing, or repeated infection affecting the bronchial mucosa causes destruction of the musculo-elastic tissue and sometimes even the cartilage with reparative replacement of these tissues by fibrous elements so that the affected section of the bronchus loses its resiliency and eventually dilates. With destruction of the mucosa there is also a loss of ciliary action and secretions normally removed from the bronchial system are retained. Thus a cess-pool is created and secondary infection is inevitable. Infection may remain localized to this area for long periods of time manifesting itself in the form of cough with purulent sputum and chronic debility and ill-health. It may, however, and it frequently does, spread out into the surrounding lung tissue producing episodes of bronchopneumonia and fibrosis of pulmonary tissue in surrounding areas. This surrounding fibrosis, as it shrinks, exerts traction influences on the already weakened bronchus inducing further dilatation.

Bronchial obstruction prevents drainage of areas distal to the site of obstruction. This results in stagnation of secretions and secondary infection which will act in the way already described. Obstruction, producing atelectasis may also possibly act in another manner. With collapse of an area of lung, the negative pressure in the pleural space is increased. As has been pointed out, the bronchial tree normally dilates on inspiration, and returns to its normal state on expiration. An increase in the negative pleural-space pressure could conceivably cause greater dilatation of the bronchial tree and prevent return to normal which might increase the tendency to bronchiectasis, though it is doubtful whether this effect is of much importance in the absence of previous bronchial weakening.

Swierenga of Holland analyzed the histories of 221 patients aged sixteen years or less who were known to be suf-

fering from bronchiectasis. One hundred and twenty-six of these children had a definite history of pneumonia, measles, whooping-cough, influenza, primary tuberculosis, intra-bronchial foreign body, or fibrocystic disease of the pancreas. In 95 cases no history of any etiologic significance in relation to bronchiectasis could be found. In discussing the latter group he points out that there is a significant relationship between the viral pneumonias and bronchiectasis. These viral pneumonias have a typical localization in the lung, involving the basal segments of the left lower lobe, the lingula of the left upper lobe, the right middle lobe, and the basal branches of the right lower lobe. This distribution is similar to that of bronchiectasis, and it has in fact been observed that irreversible bronchiectasis may follow a viral pneumonia type of illness. It is not uncommon to hear that the young patient with bronchiectasis continued to cough after a cold with no previous complaints.

The relation of constitutional defects in the bronchial walls to bronchiectasis is a matter of speculation and perhaps it will always remain so. In a few rare cases of bronchiectasis pathologists have reported an absence of cartilage in the bronchial walls. A few clinicians have tried to place the onus on allergy without much success.

Of some practical importance is the relationship of sinusitis and bronchiectasis. The two conditions frequently occur together in adults but rarely do so in children. It is believed by many that paranasal sinusitis may be a cause of, or at least an aggravating factor in the pathogenesis of bronchiectasis. Others believe there is no relationship, and there are some who believe that bronchiectasis may be responsible for many cases of sinusitis, pointing out that in their experience, resection of the diseased area of the lungs resulted in cure of sinusitis. The connection between these two conditions is therefore as yet unsettled. Many surgeons, however, advocate removal of any chronically draining upper respiratory focus of infection in addition to pulmonary resection.

Pathology

The disease may be localized to one area of lung, or it may be more generalized affecting several areas of one or both lungs. It may occur in a cylindrical form or in a saccular form, the former being the more common and frequently representing early changes, the saccular form occurring with greater frequency in the more severe grades of the condition. Its distribution is variable. The lungs may be unilaterally or bilaterally affected. There is, however, a characteristic pattern to the disease related to the facility of bronchial drainage in different parts of the lungs. Thus clinically the left lung is more often involved than the right lung in unilateral cases and the lower lobes more often than the upper lobes. Quite frequently the basal branches of the lower lobes are affected while the apical segments are free of disease. In his 221 cases, Swierenga found the disease confined to the left lung in 119 children, to the right lung in 51, and on both sides in 51.

The mucosa is at first hypertrophic but may undergo atrophy later. There may be a formation of very vascular papillary-like masses of granulation tissue which may result in bleeding. Microscopically the bronchial walls and the surrounding pulmonary tissue show chronic inflammatory change and in very advanced cases the muscle, glands, elastic tissue, and even the cartilage may be replaced by fibrous tissue.

Liebow prepared casts of the pulmonary vessels and showed that in many cases there was a great enlargement of the bronchial arteries and that an

anastomosis with the pulmonary arteries may develop. This anastomosis is at times developed to such an extent that as much as a liter of blood per minute flows through. This has the same effect as a sizeable arterio-venous shunt and increases the work-load of the left ventricle. Removal of a destroyed lung decreases this work-load.

Clinical Features:

Symptoms arise not as a result of bronchial dilatation, but rather because of associated infection.

1. *Chronic cough.*—This is usually worse in the mornings and often induced by changes in posture.

2. *Purulent sputum.*—May be copious in advanced cases, sometimes highly malodorous, and brought up in large amounts at infrequent intervals.

3. *Febrile episodes.*—These last a few days and occasionally weeks. Malaise, shivering, and night sweats may accompany the pyrexia. There may be frank episodes of pneumonia, and especially in children these episodes are sometimes found repeatedly in the same area of lung.

4. *Haemoptysis.*—This originates from the papillary granulation tissue in the affected segments of the bronchial walls. It ranges in amount from blood-stained sputum to massive haemorrhage. It may occur as the only symptom, sometimes to an alarming degree, in the absence of cough and sputum. The condition is then known as *dry bronchiectasis.*

5. *Clubbing of the fingers and toes,* decline in health, loss of weight, and night-sweating occur when the disease is attended by chronic suppuration.

Physical Signs:

Physical signs may be unilateral or bilateral, and are usually basal. Signs vary between the extremes of total absence, to signs of pneumonic infiltration with rales, to those of outright collapse and empyema.

Complications:

In the days before surgical interest in the disease and before the use of penicillin, metastatic brain abscess occurred not too infrequently and the danger of amyloid disease in longstanding cases was real. Today the complications are mainly recurrent attacks of pneumonia, secondary lung abscess, and emphysema.

Diagnosis:

A history of cough, sputum, haemoptysis, and recurrent respiratory infection often in the same area will bring to mind the possibility of bronchiectasis. The plain film of the chest is never diagnostic, but it may arouse the suspicion that the disease is present. In a majority of people suffering from bronchiectasis, and especially those with advanced disease, the plain chest film will show definite changes suggestive of the disease. However, one must remember that all types of bronchiectasis may be present despite a perfectly normal plate. Changes found are:

(1) Increased lung markings.
(2) Honeycomb-like structure.
(3) Atelectasis.
(4) Pleural changes.

Increased lung markings appear in the films as dense strands which are usually localised to the basal fields and which run as relatively broad bands most often from the hilar region down along the heart shadow. Unlike the normal vascular markings they do not end in a tapered fashion towards the periphery. They are particularly distinct in lateral views where they can be seen crossing each other and forming a net-like, coarse-meshed structure. These changes are believed to be due to severe non-specific inflammatory infil-

tration as well as peribronchial fibrosis which may extend into the pulmonary tissue.

The honeycomb-like structure appears as oval, circular, or polygonal translucencies which are surrounded by denser fibrous bands forming a dense network which reminds the observer of a honeycomb. It is likely that this structure is due to localised emphysema. The honeycomb-like structure is a reliable sign of bronchiectasis. It may appear as a manifestation of congenital cystic degeneration of the lung, which is a rare condition.

Atelectasis and pleural changes are non-specific, but when co-existing with the other changes described, they must make one suspicious.

Bronchography, by demonstrating the dilated bronchial segments is the only means of reaching an absolute diagnosis of bronchiectasis. It is used not only as a diagnostic procedure, but also to map out the extent and situation of the disease before considering therapy and carrying out surgery. It is essential in every case that the entire bronchial system in both lungs be outlined.

In addition to proving the presence of bronchiectasis, one must always remember to carry out investigations to exclude causative lesions such as tuberculosis, bronchogenic carcinoma, and intra-bronchial foreign body. The two most important investigations are bronchoscopy and examination of the sputum for tuberculosis.

The differential diagnosis includes chronic bronchitis, pulmonary tuberculosis, and lung abscess.

Treatment

The clinical manifestations of bronchiectasis are the result of anatomic changes in the lung which are irreversible. It is therefore, wherever possible, a surgical disease. Medical measures are reserved for those cases in which the disease is so extensive that surgery would not result in cure and would therefore be unwise, and for patients unable to tolerate, or who refuse to undergo thoracic surgery. Resection should seldom be undertaken in middle-aged and elderly people, particularly if emphysema is present. The best cases for surgery are those involving children or young adults with localized disease. In the graduations between these two extremes one should remember that surgery offers a cure, whereas medical treatment, once the disease is established, comes shy of removing the underlying anatomic defect. The following is an excerpt from an article by K. A. Merendino and is worth considering for it sums up well the problems imposed by bronchiectasis upon the patient. He says:

"When the disease begins early in childhood, few survive beyond the age of forty when untreated or not treated by surgical methods. Considerable impairment in the physical development begins in childhood, and chronic invalidism continues throughout life. Because of the presence of a productive cough with foul-smelling sputum, social ostracism frequently results. Eventually many develop psychological changes, varying in degree from mild depression to actual psychopathic personalities. Therefore it has become apparent that untreated and medically treated bronchiectasis is attended by a high mortality, a relatively short life expectancy, and a devastating morbidity on both a physical and a psychological basis."

Of Swierenga's 221 young patients, 176 were resected with an operative mortality in the neighbourhood of 1–2%. The results were good in 90% of cases and poor in 4%. It is his belief that surgery should be seriously considered if the disease is found to be irreversible after a sufficiently long observation period and if there are obvious clinical

complaints. Other series show less favorable results in both the operative mortality and the subsequent course of the disease. This, however, is a reflection of a less careful selection of patients suitable for surgery. In 1940 Perry and King published their observations on 400 cases they had been following and who had not been treated surgically. Though this was the era before antibiotics, the results are nevertheless interesting. Of the 400 cases, 26% were dead twenty years after the beginning of the disease. Scannel followed sixteen patients for whom surgery had been advised but not carried out. Of these sixteen, five were dead within ten years. With proper selection surgery can be undertaken today with a mortality not in excess of 2%.

The remainder of this paper will be devoted to the various forms of treatment.

MEDICAL TREATMENT

Postural coughing.—The purpose of this procedure is to keep the dilated bronchi emptied of secretion. If properly performed this may reduce sputum production by as much as 75–80%, and change a putrid pus to an odourless one. The inhalation of pancreatic enzymes such as pancreatic dornase and trypsin may also reduce the sputum and aid postural coughing by liquefaction of the sputum. They may cause undesirable side-reactions.

Bronchoscopic aspiration.—This is of value when a major bronchus is obstructed by viscid secretion and absorption collapse is present.

Antibiotics.—This form of therapy is used in combination with postural drainage. It is of great use in bringing about a reduction in the amount of sputum, in altering its composition from pus to mucus, and in removing its odour. Antibiotics are also effective for acute flare-ups. Some clinicians give antibiotics in the form of monthly injections of bicillin as a continuous prophylactic measure. Others resort to intermittent therapy to avoid the development of resistance by the bacteria. The most popular antibiotics for this purpose are penicillin, chloromycetin, and the tetracyclines.

The Medical Research Council in England carried out a trial lasting fifty-two weeks in 1957. This was a therapeutic trial designed to study the effect of prolonged antibiotic therapy in severe cases of bronchiectasis characterized by abundant purulent or mucopurulent sputum. It was carried out on an out-patients' basis with regular visits to the clinic at which time measurements were made of the volume of a twenty-four hour sputum specimen and the severity of cough, dyspnoea, haemoptysis, and disability. One hundred and twenty-two patients were followed. To one-third of this group penicillin was regularly administered, to one-third oxytetracycline, and to one-third a placebo in the form of lactose. Neither the doctor nor the patient knew what was being administered. Medical measures of treatment such as postural drainage were continued. In all groups there was a reduction in sputum volume greater for the pus than the mucus fraction. In the oxytetracycline group there was a reduction in volume to 50% of the pretreatment level; while in the penicillin and lactose group the reduction was to 70%. A more pronounced effect was observed in the oxytetracycline group in the reduction of disability expressed by the number of days off work, in the episodes of fever, and in the number of days confined to bed.

SURGICAL TREATMENT

There is no place for a description of the operative surgery involved in the treatment of bronchiectasis in this paper. Suffice it to say that bronchiectasis is

very suitable for segmental resection, and that the object of surgical treatment is the removal of all diseased tissue, leaving behind completely healthy lung tissue. In selected cases the results are excellent and wherever feasible, surgery should be undertaken.

Bibliography

1. Best & Taylor: The Physiol. Basis of Med. Practice. Ed. 6, pp. 359.
2. Swierenga, J.: Bronchiectasis—Dis. of the Chest. August, 1957.
3. Boyd, W.: Textbook of Pathology. Ed. 6.
4. Liebow: Bronchiectasis—Am. J. Path. 1949.
5. Davidson, L. S. P.: Principles and Practice of Medicine. Ed. 3.
6. Gudbjerg, C. E.: Bronchiectasis; Radiological Diagnosis and Prognosis after Operative Treatment—Acta Radiologica, Supp. 143. 1957.
7. Merendino, A. K.: Pr. and Pract. of Surg.: Allen, Moyer, Harkins, and Rhoads. Ed. 2.
8. The Committee of the Medical Research Council: Prolonged Antibiotic Treatment of severe Bronchiectasis, a report by a subcommittee—Brit. Med. J., Aug. 3, 1957.

EMBERS

The halls are empty with terrible echoes
Which resound the mournful wailing from the long ward;
Row upon row, disease abides its time
Eroding into the flesh of men, whose hollow eyes stare up into a hopeless gourd.

A proud head with greying temples
Falls upon a weightless pillow
And buries his eyes in the downy fluff
And remembers the rue of the burdened willow.

The dancing jig of spastic fingers reaching for the side
Ebbs and flickers in nervous ecstasy for the plastic cup of tepid water
Which tremorously is slowly brought to parched lips
To be gummed by the toothless devil whose bond with life does totter.

Mad eyes thrash to and fro in the bleak white of sick bulbs,
Desperately searching for that holy miracle to restore that spring of health;
Despondent eyes, whose own circuitous travels bespeak this sad futility;
But naught is theirs, for my scientific wit can only fool but not destroy the fermentation of their soul.

C.S.S.

ABSTRACTS

SURGICAL MANAGEMENT OF DIVERTICULITIS OF THE SIGMOID COLON. S. E. O'Brien and K. I. Mustard. The Canadian Medical Association Journal: 4, 80, 1959.

Diverticulitis may resolve or develop certain complications such as perforation with peritonitis or localized abscess, internal and external fistulae, and fibrosis with stenosis and large bowel obstruction.

The disease usually presents with one of these clinical pictures: (1) Recurring lower abdominal pain and constipation and tender mass. (2) Large bowel obstruction. (3) Peritonitis. (4) Urinary symptoms suggesting vesico-colic fistula. (5) Rectal bleeding. Correct preoperative diagnosis is often difficult with acute appendicitis and carcinoma being the most common to be confused.

Until recently surgery was only employed to treat serious complications, and there was a high recurrence of diverticulitis. It is now widely believed that resection of the diseased segment is necessary. A one-stage or multiple-stage operation can be used. If resection is hazardous a preliminary colostomy is done, with resection and anastomosis of the sigmoid six months later, and the closing of the colostomy being the third stage.

In patients in good general condition, without complications, and a well prepared colon a one-stage operation can be performed. It is hoped in the future that patients will be referred earlier for surgical treatment so that the one-stage procedure with its shorter period of morbidity can be more often used.

AMINOPHYLLINE POISONING IN CHILDREN. H. L. Bacal *et al.*, The Canadian Medical Association Journal, 80: 6, 1959.

Aminophylline (theophylline ethylinediamine) is valuable in the management of bronchial asthma since it causes relaxation of the smooth muscles of the bronchi. Its effect is cumulative and is synergistic with ephedrine. Other effects of the drug include central nervous system stimulation, increased gastric secretion, diuresis, and both central and peripheral action on the cardiovascular system.

Clinical manifestations of overdosage may be: (1) restlessness and irritability which may progress to convulsions and coma; (2) nausea, vomiting, or even hematemesis; (3) diuresis with albuminuria and dehydration; and (4) cardiovascular collapse.

The following doses are recommended for children:

(a) Oral: 5 mg./kg. q. 6–8 h.

(b) Rectal: 7 mg./kg. q. 6–8 h. where oral administration is not practicable.

PROPHYLAXIS OF RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE. Joseph M. Miller, The New England Journal of Medicine, 260: 220, 1959.

Since practically all attacks of rheumatic fever are preceded by group A hemolytic streptococcal infections, an accurate diagnosis and adequate treatment of these infections are important in its prevention. Prompt use of penicillin eradicates the streptococcal infection and also suppresses the antibody response.

Previous attacks of rheumatic fever predispose to recurrences and continues penicillin prophylaxis is successful in preventing recurrent streptococcal infections.

Sulphonamides have not been found effective in inhibiting the antibody response, but are useful in the prophylaxis of streptococcal infections.

The duration of prophylactic therapy is still open to question, but at present it is most advantageous to continue it for twenty years after the initial attack and also during the childbearing period.

Bacterial resistance and superinfection have not been problems in this long-term prophylaxis.

R.F.A.

NEWS AND NOTES

At the annual social function of the Council of the Academy of Medicine on April 7, Dr. Margaret G. Norman, 5T8, will be presented with a cheque for $50.00 having won the Webster scholarship for her article "Diabetes Mellitis in Pregnancy" which appeared in Volume XXXV of the University of Toronto Medical Journal.

Through the generosity of the late Dr. Robert Thomas Noble, who graduated from the University of Toronto in 1895, and was for many years the Registrar of the College of Physicians and Surgeons of Ontario, a bequest has been made to the Medical Library of the University of Toronto. The interest from the fund, which was given in memory of the Class in Medicine of 1895, is to be used for the purchase of books and periodicals for the Medical Library.

COMPREHENSIVE ATTACK

on the causative factors in

PEPTIC ULCER

"RESTROPIN" BRAND COMPOUND

presents three therapeutic agents:

ANTISECRETORY

Methscopolamine nitrate — one of the most potent antispasmodic and antisecretory parasympatholytic compounds shown to be clinically selective and effective.

ANTACID

Aluminum glycinate — a stable, non-absorbable, acid-neutralizing agent with a prompt and prolonged effect.

SEDATIVE

Butabarbital — a non-cumulative sedative which, in small doses, reduces sensitivity to disturbing situations of daily life without seriously impairing efficiency.

Each tablet contains:

Methscopolamine nitrate 2.5mg.(1/25gr.)
Aluminum glycinate,basic* 0.5G.(7½ gr.)
Butabarbital NND..... 16 mg. (¼ gr.)

**Patented, 1951.*

DOSAGE: One tablet before each meal and one or two tablets at bedtime.

Bottles of 100 tablets

CAUTION: Preparations containing methscopolamine nitrate are contraindicated in patients with certain types af cardiac arrhythmias. When the recommended dosage has been exceeded, and in some patients on average therapeutic doses, one or more of the following side effects have been nated: dryness of the mouth, visual blurring, constipatian, difficulty in starting urinatian, weakness and headache. Under these circumstances the dose should be reduced.

Charles E. Frosst & Co.
MONTREAL CANADA

PROMOTES
"A SENSE OF WELL-BEING"

*"Premarin"**

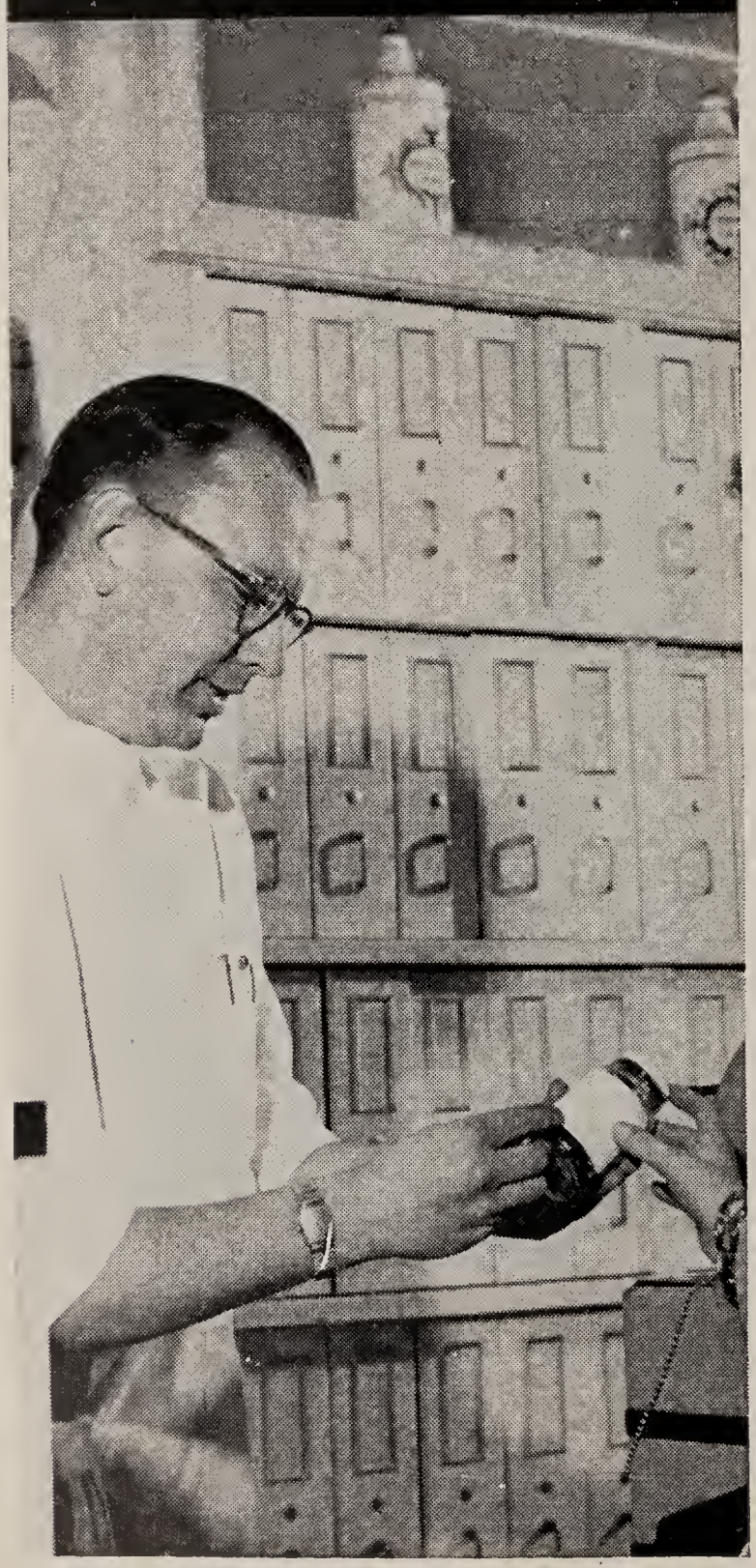
for dramatic relief from
SYMPTOMS OF THE MENOPAUSE

*This complete natural estrogen complex is available in various formulae and potencies — in tablet form and in combination with meprobamate and methyltestosterone.

Ayerst *Ayerst, McKenna & Harrison Limited, Montreal*

95-259

this is your Professional Helper



. . . when the Pharmacist does ALL your dispensing

The years he has spent at his College of Pharmacy and in actual experience, qualify him to render you expert assistance in all things pharmaceutical, leaving you more time for enlarging your practice, for studying or for leisure.

ONTARIO RETAIL PHARMACISTS' ASSOCIATION

THE ONTARIO RETAIL PHARMACISTS' ASSOCIATION

"Think we should tell our doctor?

"Certainly! He'll want to know about the two New Farmer's Wife Prepared Formulas with Vitamin C added!

Farmer's Wife Infant Formula Milks have been consistently first in every major infant feeding development. Now Farmer's Wife is first again, with a stable form of Vitamin C (5.0 mg. per fl. oz.) in its two new "Instant" Prepared Formulas:

1. Farmer's Wife Red Band Prepared Formula, made from whole milk, with added carbohydrate, and Vitamins C and D. (6.5% Butterfat)

2. Farmer's Wife Blue Band Prepared Formula, made from partly skimmed milk, with added carbohydrate, and Vitamins C and D. (4% Butterfat).

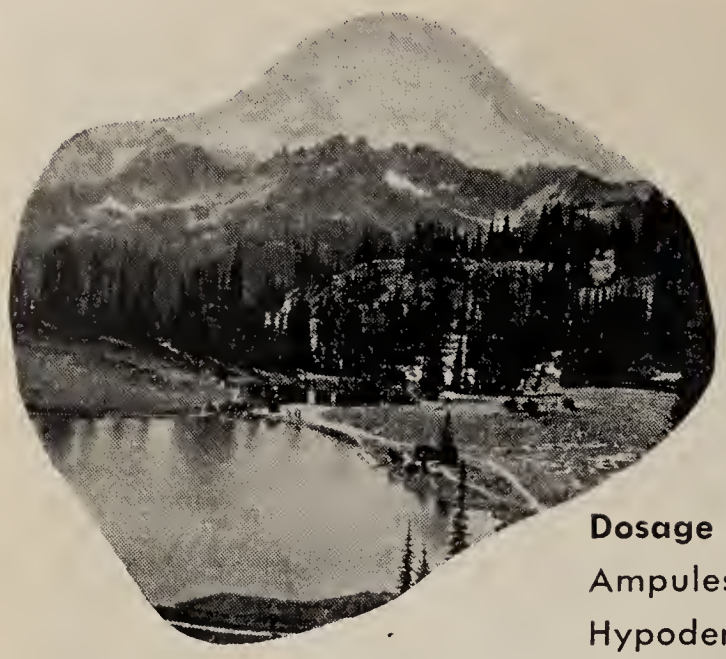
These two new Prepared Formulas eliminate the chance of contamination or error in formula preparation. They save mothers time, trouble and expense.

Farmer's Wife is also available in the original three strengths—Whole Milk, Partly Skimmed and Skimmed Milk.

Farmer's Wife

Prescribed by doctors—
Approved by mothers

for the peak of analgesic efficiency



DILAUDID ®

brand of DIHYDROMORPHINONE

Dosage Forms of Dilaudid hydrochloride:

Ampules: 1 cc., 2 mg. each.

Hypodermic Tablets: 2 and 4 mg. each.

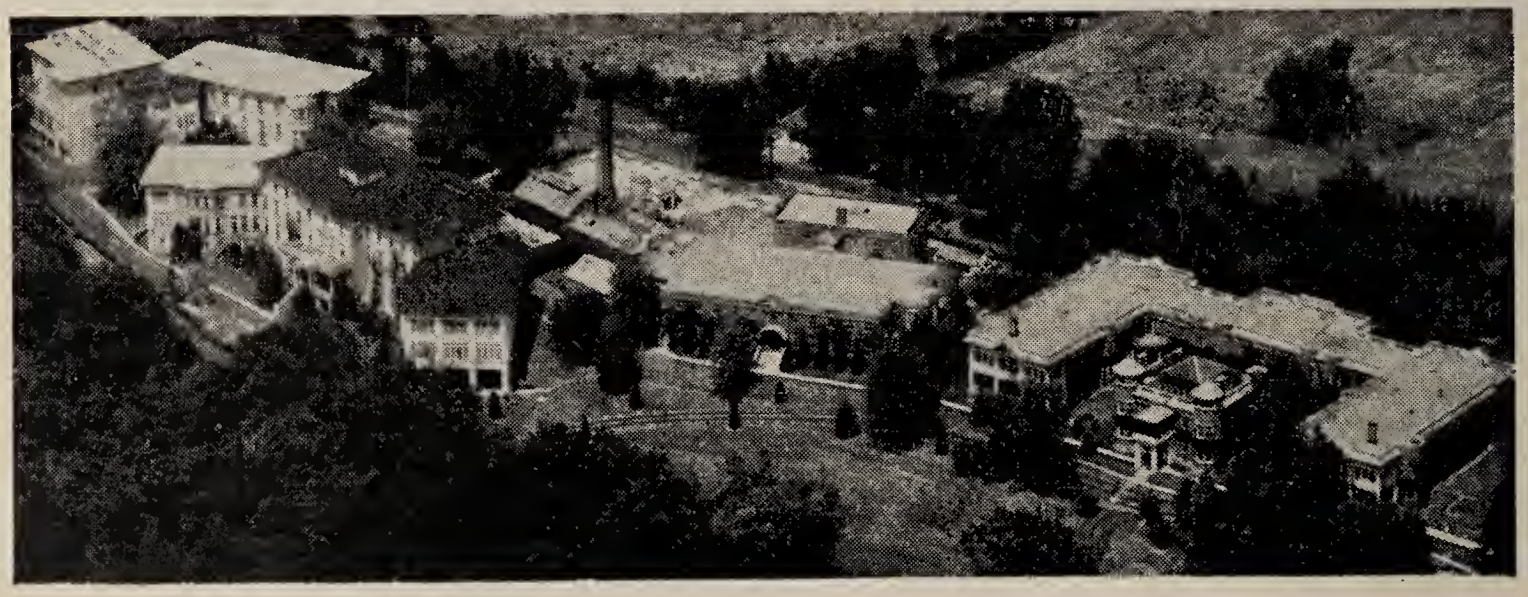
Oral Tablets: 2.7 mg. each.

Multiple Dose Vial: 10 cc., 2 mg. Dilaudid sulfate per cc.

Dilaudid, Trademark reg., marketed by Knoll Pharmaceutical Company, Orange, N. J.

MERCK & CO. Limited *exclusive distributor*

MONTREAL TORONTO VANCOUVER VALLEYFIELD



Homewood Sanitarium

A private hospital for the diagnosis, care and treatment of all types of psychiatric disorders. An adequate staff of specialists study each patient carefully and fit the treatment to his individual needs. Excellent cuisine, comfortable accommodation and personal attention of specially trained nursing staff contribute to the recovery of the patient. All types of modern therapy are available, including Psychotherapy, Insulin and Electro-shock, combined with excellent Occupational and Recreational facilities. The Sanitarium buildings, accommodating 225 patients, are situated in a very attractive setting within the confines of the City of Guelph.

Homewood has been approved as a private hospital under the Ontario Hospital Insurance Plan. Benefits depend on type of illness and other factors. oFr full information write or telephone (TAylor 4–1010).

A. L. MacKINNON, M.B., Medical Supt.

THE HOMEWOOD SANITARIUM OF GUELPH, ONTARIO, LIMITED

In prescribing for control....

Ortho offers
the advantage
of choice
to meet the
different needs
of individual
patients

when
a
cream
alone is
preferred

Ortho

*Trade Mark

ORTHO PHARMACEUTICAL (CANADA) LTD.
TORONTO, ONT.